REMARKS

The title has been amended to correct a typographical error.

The Specification has been amended in accordance with 37 CFR §1.78 to make reference to the International Application from which this application originates and to incorporate by reference the Danish priority applications. The Specification has also been amended to correct informalities and typographical errors. A mark up copy and a clean copy of the substitute specification are provided. No new matter has been added by the amendments.

The claims have been amended to correct informalities, and to eliminate multiple dependencies. The amendment is made to reduce filing fees and not for any other reason related to patentability of such claims. Claims 34 - 37 have been added to restore the subject matters that were removed as a result of the amendment, and to further claim what Applicants regard as their invention. No new matter has been added by the amendments.

The Abstract has been amended to correct informalities. No new matter has been added by the amendments.

The claim fee was calculated based on the amended claims above. Please examine the application in view of the amendments set forth above.

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Respectfully submitted,

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DIPHENYL ~~OX INDOL 2 ONOX INDOL-2-ONE~~ COMPOUNDS AND THEIR USE IN THE TREATMENT OF CANCER

CROSS-REFERENCE TO PRIOR APPLICATIONS

This application is a U.S. national phase application under 35 U.S.C. §371 of International Patent Application No. PCT/DK2005/000244, filed April 8, 2005, and claims the benefit of Danish Application No. 2004 00576, filed April 8, 2004; Danish Application No. 2004 00693, filed May 1, 2004; Danish Application No. 2004 01153, filed July 27, 2004; and Danish Application No. 2004 01216, filed August 11, 2004, all of which are incorporated by reference herein. The International Application was published in English on October 20, 2005 as International Publication No. WO 2005/097107 under PCT Article 21(2).

FIELD OF THE INVENTION

The present invention relates to substituted 3,3-diphenyl-1,3-dihydro-indol-2-one compounds, and the use of such compounds for the preparation of a medicament for the treatment of cancer in a mammal.

BACKGROUND OF THE INVENTION

US 1,624,675 describes O-O-diacyl derivatives of diphenolisatine and that these compounds possess laxative properties.

While inhibition of protein synthesis inhibits cell proliferation, highly proliferative cancer cells may be more sensitive than normal cells to protein synthesis inhibition because many oncogenes and growth regulatory proteins required for effective cell proliferation are encoded by inefficiently translated mRNAs, and are dependent on eukaryotic translation initiation factors (Aktas et al. (1998) Proc Natl Acad Sci 95, 8280 and references therein).

Protein synthesis is regulated in response to cell stress, which can be induced by environmental or physiological challenges (such as hypoxia, amino acid or nutrient deprivation), intracellular calcium load and protein glycosylation inhibition. For example, cell stressors such as clotrimazole, 3,3-diphenyloxindole, thapsigargin, tunicamycin and arsenite (Aktas et al. (1998) Proc Natl Acad Sci 95, 8280; Brewer et al. (1999) Proc Natl Acad Sci 96,

8505-8510; Harding et al. (2000) Molecular Cell 5, 897-904; Natarajan et al. (2004) J Med Chem 47, 1882-1885) act as protein translation initiation inhibitors, reducing both protein synthesis and cell proliferation.

The possibility that protein translation initiation inhibiters may have potential as anti-cancer drugs has been described previously (Aktas et al. (1998) Proc Natl Acad Sci 95; Natarajan et al. (2004) J.Med.Chem 47, 1882-1885; Natarajan et al. (2004) J.Med.Chem 47, 4979-4982). The Natarajan papers further disclose 3,3-diaryl-1,3-dihydroindol-2-ones which potentially inhibit protein translation.

Protein synthesis is also regulated by the mTOR pathway, providing another link to a nutrient and amino acid status (Harris & Lawrence (2003) ScienceSTKE (212) re15; Nave et al. (1999) Biochem J 344, 427; Beaunet et al. (2003) Biochem J 372, 555-566; Inoki et al. (2003) Cell 115, 577-590). This pathway is also linked to regulation of the protein translation initiation complex (Cherkasova & Hinnebusch (2003) Genes & Dev 17, 859-872; Kubota et al. (2003) J Biol Chem 278, 20457). Inhibition of mTOR signalling inhibits the proliferation of cancer cell lines (Noh et al. (2004) Clinical Cancer Research 10, 1013-1023; Yu et al. (2001) Endocrine-Related Cancer 8, 249-258), and has been proposed as a target for cancer therapy (Huang & Houghton (2003) Curr Opin Pharmacol 3, 371-377).

The lead compound among the 3,3-diaryl-1,3-dihydroindol-2-one compounds of the earliest Natarajan et al. paper (Natarajan et al. (2004) J.Med.Chem 47, 1882-1885) is 3-(2-hydroxy-5-t-butyl-phenyl)-3-phenyl-1,3-dihydroindol-2-one.

US 2004/0242563 A1 discloses substituted diphenyl indanone, indane and indole compounds and analogues thereof useful for the treatment or prevention of diseases characterized by abnormal cell proliferation.

However, there is still a need for improved compounds capable of inhibiting the uncontrolled growth of cancer cells, in particular compounds exhibiting selective cancer cell proliferation inhibition.

SUMMARY OF THE INVENTION

The present invention relates to the use of a hitherto sparsely studied subclass of 3,3-diphenyl-1,3-dihydroindol-2-one compounds in which the phenyl moieties are para-substituted via particular heteroatoms, in particular via oxygen atoms, in particular carrying hydroxy groups.

Thus, one aspect of the present invention relates to the use of a compound of the general formula (I) as defined herein for preparation of a medicament for the treatment of cancer in a mammal~~, cf. claim 1~~.

Another aspect of the present invention relates to a compound as defined herein for use as a medicament, with the proviso that the compound is not one selected from 3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one and acetic acid 4-[3-(4-acetoxy-phenyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-phenyl ester~~, claims 30~~.

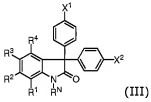
A further aspect of the present invention relates to a novel compound of the general formula (I) or (II)~~, cf. claims 31 and 32~~.

A still further aspect of the present invention relates to a pharmaceutical composition~~, cf. claim 33~~.

An even further aspect of the present invention relates to a method of treating a mammal suffering from or being susceptible to cancer.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: shows results from the cell proliferation studies using the compounds described in the Examples section corresponding to the following formula (III) (Example 2):



(III)

Figure 2: shows results of the protein synthesis experiments using compound 3 in the MDA-468 and MDA-231 human breast cancer cell lines (Example 3).

Figure 3: illustrates Translational Control pathways (from the Cell Signaling Technology catalogue 2003-2004).

Figure 4: shows Western Blots on proteins involved in translational control using MDA-468 cells (24 hour compound incubation). 1: DMSO (0.08%); 2: Compound 3 (200 nM); ~~3~~2:

Compound 3 (2 μM); 4: other (2 μM); 5: Rapamycin (100 nM); and 6: LY294002 (10 μM) (Example 4).

Figure 5: shows Western Blots on proteins involved in translational control comparing MDA-468 & MDA-231 cells (48 hours incubation). 1: DMSO (0.08%); 2: Compound 3 (200 nM); 4: other (2 μM); 5: Rapamycin (100 nM); and 6: LY294002 (10 μM) (Example 4).

Figure 6: illustrates the results of PC3M human prostate cancer cell xenograft experiments using Compound 3 (Example 5).

Figure 7: shows the effect of Compound 3 in a cell proliferation assay using a panel of human breast cancer cell lines in medium containing 1% FBS. PCTACT corresponds to growth inhibition relative to 50 μM terfenidine (100 PCTACT) (Example 6).

Figure 8: shows the effect of Compound 3 on proliferation of the non-transformed human breast epithilial cell line MCF10A. PCTACT corresponds to growth inhibition relative to 50 μM terfenidine (100 PCTACT) (Example 6).

Figure 9: shows the effect of Compound 3 in a cell proliferation assay using a panel of human breast cancer cell lines in medium containing 10% FBS. PCTACT corresponds to growth inhibition relative to 50 μM terfenidine (100 PCTACT) (Example 6).

Figure 10: shows the effect of Compound 21 in a cell proliferation assay using a panel of breast cancer cell lines in medium containing 10% FBS (except MCF10A that is grown in serum-free MEGM medium). PCTACT corresponds to growth inhibition relative to 50 μM terfenidine (100 PCTACT) (Example 6).

Figure 11: shows the effect of oxyphenisatine in a cell proliferation assay using a panel of breast cancer cell lines in medium containing 10% FBS (except MCF10A that is grown in serum-free MEGM medium). PCTACT corresponds to growth inhibition relative to 50 μM terfenidine (100 PCTACT) (Example 6).

Figure 12: shows the effect of Compounds 3 and 21, and oxyphenisatine in a cell proliferation assay using a panel of prostate cancer cell lines in medium containing 10% FBS. PCTACT corresponds to growth inhibition relative to 50 μM terfenidine (100 PCTACT) (Example 6).

Figure 13: shows the effect of Compounds 3 and 41 in a cell proliferation assay using PC3 prostate cancer cell lines in medium containing 10% FBS (Example 6).

Figure 14: shows the results of the cell proliferation assay showing effect of Compound 3 on the colon cancer cell line Colo205 in medium containing 10% FBS. PCTACT corresponds to growth inhibition relative to 50 μM terfenidine (100 PCTACT) (Example 6).

Figure 15: illustrates that Compound 3 reduces the rate of MDA-MB-468 tumour cell growth in xenograft experiments in a dose related manner when given as a monotherapy either by the PO or IV route. Furthermore, tumour regression is noted using the higher doses of Compound 3 (Example 7).

Figure 16: illustrates that Compound 41 reduces the rate of MDA-MB-468 human breast cancer tumour cell growth in xenograft experiments and induces tumour regression at all doses tested when given as a monotherapy either by the PO or IV route. The effect is more pronounced than following administration of paclitaxel (Example 7).

Figure 17: illustrates that Compound 41 reduces the rate of MCF-7 human breast cancer tumour cell growth in xenograft experiments and induces tumour regression at all doses tested when given as a monotherapy either by the PO or IV route. The effect is more pronounced than following administration of paclitaxel (Example 8).

Figure 18: illustrates that Compound 3 activates caspase activity in most human breast cancer cell lines, indicating that the compound exhibits pro-apoptotic activity (Example 9).

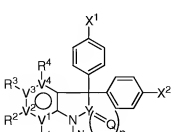
DETAILED DESCRIPTION OF THE INVENTION

Compounds for the treatment of cancer in a mammal

One aspect of the present invention relates to particular compounds for the preparation of a medicament for the treatment of cancer in a mammal.

The term cancer is typically describing cell growth not under strict control. In one embodiment of the invention, treatment of cancers is provided in which inhibition of protein synthesis and/or inhibition of activation of the mTOR pathway is an effective method for reducing cell growth. Examples of such cancers are breast cancer, renal cancer, multiple myeloma, leukemia, glio blastoma, rhabdomyosarcoma, prostate, soft tissue sarcoma, colorectal sarcoma, gastric carcinoma, head and neck squamous cell carcinoma, uterine, cervical, melanoma, lymphoma, and pancreatic cancer.

The useful compounds have the general formula (I), namely



(I)

wherein

V^1, V^2, V^3, and V^4 independently are selected from a carbon atom, a non-quaternary nitrogen atom, an oxygen atom, and a sulfur atom, and where V^4 further may be selected from a bond, so that $-V^1-V^2-V^3-V^4-$ together with the atoms to which V^1 and V^4 are attached form an aromatic or heteroaromatic ring;

R^1, R^2, R^3, and R^4, when attached to a carbon atom, independently are selected from hydrogen, optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl, hydroxy, optionally substituted C_{1-6}-alkoxy, optionally substituted C_{2-6}-alkenyloxy, carboxy, optionally substituted C_{1-6}-alkoxycarbonyl, optionally substituted C_{1-6}-alkylcarbonyl, optionally substituted C_{1-6}-alkylcarbonyloxy, formyl, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylsulphonylamino, cyano, carbamido, mono- and di(C_{1-6}-alkyl)aminocarbonylamino, C_{1-6}-alkanoyloxy, C_{1-6}-alkylsulphonyl, C_{1-6}-alkylsulphinyl, aminosulfonyl, mono- and di(C_{1-6}-alkyl)aminosulfonyl, nitro, optionally substituted C_{1-6}-alkylthio, aryl, aryloxy, arylcarbonyl, arylamino, heterocyclyl, heterocyclyloxy, heterocyclylamino, heterocyclylcarbonyl, heteroaryl, heteroaryloxy, heteroarylamino, heteroarylcarbonyl, and halogen, where any C_{1-6}-alkyl as an amino substituent is optionally substituted with hydroxy, C_{1-6}-alkoxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylaminocarbonyl, or halogen(s), and wherein any aryl, heterocyclyl and heteroaryl may be optionally substituted;

R^1, R^2, R^3, and R^4, when attached to a nitrogen atom, independently are selected from hydrogen, optionally substituted C_{1-6}-alkyl, hydroxy, optionally substituted C_{1-6}-alkoxy, optionally substituted C_{1-6}-alkoxycarbonyl, optionally substituted C_{1-6}-alkylcarbonyl, formyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino, C_{1-6}-alkylcarbonylamino, mono- and di(C_{1-6}-alkyl)amino, C_{1-6}-alkylsulphonyl, C_{1-6}-alkylsulphinyl, aryl, aryloxy, arylcarbonyl, arylamino, heterocyclyl, heterocyclyloxy, heterocyclylcarbonyl, heterocyclylamino, heteroaryl, heteroaryloxy, heteroarylcarbonyl, and heteroarylamino; where any C_{1-6}-alkyl as an amino

substituent is optionally substituted with hydroxy, C_{1-6}-alkoxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylaminocarbonyl, or halogen(s), and wherein any aryl, heterocyclyl and heteroaryl may be optionally substituted;

or R^1 and R^2 together with the carbon atoms to which they are attached form a ring, e.g. an aromatic ring, a carbocyclic ring, a heterocyclic ring or a heteroaromatic ring, in particular an aromatic ring, a heterocyclic ring or a heteroaromatic ring;

X^1 and X^2 are independently selected from halogen, hydroxy, optionally substituted C_{1-6}-alkoxy, optionally substituted C_{1-6}-alkylcarbonyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylsulphonylamino, mono- and di(C_{1-6}-alkyl)amino-carbonylamino, C_{1-6}-alkanoyloxy, mercapto, optionally substituted C_{1-6}-alkylthio, C_{1-6}-alkylsulfonyl, mono- and di(C_{1-6}-alkyl)aminosulfonyl, aryloxy, arylamino, heterocyclyloxy, heterocyclylamino, heteroaryloxy and heteroarylamino, where any C_{1-6}-alkyl as an amino or sulphur substituent is optionally substituted with hydroxy, C_{1-6}-alkoxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylaminocarbonyl, or halogen(s), and wherein any aryl, heterocyclyl and heteroaryl may be optionally substituted;

$>Y(=Q)_n$ is selected from >C=O, >C=S, >S=O and $>S(=O)_2$; and

R^N is selected from the group consisting of hydrogen, optionally substituted C_{1-6}-alkyl, hydroxy, optionally substituted C_{1-6}-alkoxy, optionally substituted C_{1-6}-alkoxycarbonyl, optionally substituted C_{1-6}-alkylcarbonyl, formyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino, C_{1-6}-alkylcarbonylamino, mono- and di(C_{1-6}-alkyl)amino, C_{1-6}-alkylsulphonyl, and C_{1-6}-alkylsulphinyl; where any C_{1-6}-alkyl as an amino substituent is optionally substituted with hydroxy, C_{1-6}-alkoxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylaminocarbonyl, or halogen(s).

Also included in the class of compounds of the formula (I) are pharmaceutically acceptable salts and prodrugs thereof.

One variant of the compounds of the formula (I) ~~are~~includes those wherein each of the benzene rings to which X^1 and X^2 are attached further may be substituted with one, two, three or four fluoro atoms, in particular each benzene ring to which X^1 and X^2 are attached ~~are~~is substituted with two fluoro atoms in the ortho positions relative to the substituents X^1 and X^2, respectively.

Definitions

In the present context, the term "C_{1-6}-alkyl" is intended to mean a linear, cyclic or branched hydrocarbon group having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, *iso*-propyl, pentyl, cyclopentyl, hexyl, cyclohexyl, and the term "C_{1-4}-alkyl" is intended to cover linear, cyclic or branched hydrocarbon groups having 1 to 4 carbon atoms, e.g. methyl, ethyl, propyl, *iso*-propyl, cyclopropyl, butyl, *iso*-butyl, *tert*-butyl, cyclobutyl.

Similarly, the term "C_{2-6}-alkenyl" is intended to cover linear, cyclic or branched hydrocarbon groups having 2 to 6 carbon atoms and comprising one unsaturated bond. Examples of alkenyl groups are vinyl, allyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, heptadecaenyl. Preferred examples of alkenyl are vinyl, allyl, butenyl, especially allyl.

In the present context, i.e. in connection with the terms "alkyl", "alkoxy", and "alkenyl", the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-3 times, with group(s) selected from hydroxy (which when bound to an unsaturated carbon atom may be present in the tautomeric keto form), C_{1-6}-alkoxy (i.e. C_{1-6}-alkyl-oxy), C_{2-6}-alkenyloxy, carboxy, oxo (forming a keto or aldehyde functionality), C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylcarbonyl, formyl, aryl, aryloxy, arylamino, arylcarbonyl, aryloxycarbonyl, arylcarbonyloxy, arylaminocarbonyl, arylcarbonylamino, heteroaryl, heteroaryloxy, heteroarylamino, heteroarylcarbonyl, heteroaryloxycarbonyl, heteroarylcarbonyloxy, heteroarylaminocarbonyl, heteroarylcarbonylamino, heterocyclyl, heterocyclyloxy, heterocyclylamino, heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylcarbonyloxy, heterocyclylaminocarbonyl, heterocyclylcarbonylamino, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkylcarbonylamino, cyano, guanidino, carbamido, C_{1-6}-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C_{1-6}-alkanoyloxy, C_{1-6}-alkyl-sulphonyl, C_{1-6}-alkyl-sulphinyl, C_{1-6}-alkylsulphonyloxy, nitro, C_{1-6}-alkylthio, and halogen, where any aryl, heteroaryl and heterocyclyl may be substituted as specifically described below for aryl, heteroaryl and heterocyclyl, and any alkyl, alkoxy, and the like, representing substituents may be substituted with hydroxy, C_{1-6}-alkoxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylaminocarbonyl, or halogen(s).

Typically, the substituents are selected from hydroxy (which when bound to an unsaturated carbon atom may be present in the tautomeric keto form), C_{1-6}-alkoxy (i.e. C_{1-6}-alkyl-oxy), C_{2-6}-alkenyloxy, carboxy, oxo (forming a keto or aldehyde functionality), C_{1-6}-alkylcarbonyl, formyl, aryl, aryloxy, arylamino, arylcarbonyl, heteroaryl, heteroaryloxy, heteroarylamino, heteroarylcarbonyl, heterocyclyl, heterocyclyloxy, heterocyclylamino, heterocyclylcarbonyl, amino, mono- and di(C_{1-6}-alkyl)amino; carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl,

amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, guanidino, carbamido, C_{1-6}-alkyl-sulphonyl-amino, C_{1-6}-alkyl-sulphonyl, C_{1-6}-alkyl-sulphinyl, C_{1-6}-alkylthio, halogen, where any aryl, heteroaryl and heterocyclyl may be substituted as specifically described below for aryl, heteroaryl and heterocyclyl.

In some embodiments, substituents are selected from hydroxy, C_{1-6}-alkoxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylaminocarbonyl, or halogen.

The term "Halogen""halogen" includes fluoro, chloro, bromo, and iodo.

In the present context, the term "aryl" is intended to mean a fully or partially aromatic carbocyclic ring or ring system, such as phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, anthracyl, phenanthracyl, pyrenyl, benzopyrenyl, fluorenyl and xanthenyl, among which phenyl is a preferred example.

The term "heteroaryl" is intended to mean a fully or partially aromatic carbocyclic ring or ring system where one or more of the carbon atoms have been replaced with heteroatoms, e.g. nitrogen (=N- or –NH-), sulphur, and/or oxygen atoms. Examples of such heteroaryl groups are oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, coumaryl, furanyl, thienyl, quinolyl, benzothiazolyl, benzotriazolyl, benzodiazolyl, benzooxozolyl, phthalazinyl, phthalanyl, triazolyl, tetrazolyl, isoquinolyl, acridinyl, carbazolyl, dibenzazepinyl, indolyl, benzopyrazolyl, phenoxazonyl. Particularly interesting heteroaryl groups are benzimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, furyl, thienyl, quinolyl, triazolyl, tetrazolyl, isoquinolyl, indolyl in particular benzimidazolyl, pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, furyl, thienyl, quinolyl, tetrazolyl, and isoquinolyl.

The term "heterocyclyl" is intended to mean a non-aromatic carbocyclic ring or ring system where one or more of the carbon atoms have been replaced with heteroatoms, e.g. nitrogen (=N- or –NH-), sulphur, and/or oxygen atoms. Examples of such heterocyclyl groups (named according to the rings) are imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, aziridine, azirine, azetidine, pyroline, tropane, oxazinane (morpholine), azepine, dihydroazepine, tetrahydroazepine, and hexahydroazepine, oxazolane, oxazepane, oxazocane, thiazolane, thiazinane, thiazepane, thiazocane, oxazetane, diazetane, thiazetane, tetrahydrofuran, tetrahydropyran, oxepane, tetrahydrothiophene, tetrahydrothiopyrane,

thiepane, dithiane, dithiepane, dioxane, dioxepane, oxathiane, oxathiepane. The most interesting examples are tetrahydrofuran, imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, azetidine, tropane, oxazinane (morpholine), oxazolane, oxazepane, thiazolane, thiazinane, and thiazepane, in particular tetrahydrofuran, imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, pyrrolidine, piperidine, azepane, oxazinane (morpholine), and thiazinane.

In the present context, i.e. in connection with the terms "aryl", "heteroaryl", "heterocyclyl" and the like (e.g. "aryloxy", "heterarylcarbonyl", etc.), the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-5 times, in particular 1-3 times, with group(s) selected from hydroxy (which when present in an enol system may be represented in the tautomeric keto form), C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, oxo (which may be represented in the tautomeric enol form), carboxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylcarbonyl, formyl, aryl, aryloxy, arylamino, aryloxycarbonyl, arylcarbonyl, heteroaryl, heteroarylamino, amino, mono- and di(C_{1-6}-alkyl)amino; carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, cyano, guanidino, carbamido, C_{1-6}-alkanoyloxy, C_{1-6}-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C_{1-6}-alkyl-suphonyl, C_{1-6}-alkyl-sulphinyl, C_{1-6}-alkylsulphonyloxy, nitro, sulphanyl, amino, amino-sulfonyl, mono- and di(C_{1-6}-alkyl)amino-sulfonyl, dihalogen-C_{1-4}-alkyl, trihalogen-C_{1-4}-alkyl, halogen, where aryl and heteroaryl representing substituents may be substituted 1-3 times with C_{1-4}-alkyl, C_{1-4}-alkoxy, nitro, cyano, amino or halogen, and any alkyl, alkoxy, and the like, representing substituents may be substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino, or guanidino.

Typically, the substituents are selected from hydroxy, C_{1-6}-alkyl, C_{1-6}-alkoxy, oxo (which may be represented in the tautomeric enol form), carboxy, C_{1-6}-alkylcarbonyl, formyl, amino, mono- and di(C_{1-6}-alkyl)amino; carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, guanidino, carbamido, C_{1-6}-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C_{1-6}-alkyl-suphonyl, C_{1-6}-alkyl-sulphinyl, C_{1-6}-alkylsulphonyloxy, sulphanyl, amino, amino-sulfonyl, mono- and di(C_{1-6}-alkyl)amino-sulfonyl or halogen, where any alkyl, alkoxy and the like, representing substituents may be substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino, or guanidino. In some embodiments, the substituents are selected from C_{1-6}-alkyl, C_{1-6}-alkoxy, amino, mono- and di(C_{1-6}-alkyl)amino, sulphanyl, carboxy or halogen, where any alkyl, alkoxy and the like, representing substituents may be substituted with

hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino, or guanidino.

The term "prodrug" used herein is intended to mean a derivative of a compound of the formula (I) which – upon exposure to physiological conditions – will liberate a compound of the formula (I) which then will be able to exhibit the desired biological action. Examples of prodrugs are esters (carboxylic acid ester, phosphate esters, sulphuric acid esters, etc.), acid labile ethers, acetals, ketals, etc.

The term "pharmaceutically acceptable salts" is intended to include acid addition salts and basic salts. Illustrative examples of acid addition salts are pharmaceutically acceptable salts formed with non-toxic acids. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric acids. Examples of basic salts are salts where the (remaining) counter ion is selected from alkali metals, such as sodium and potassium, alkaline earth metals, such as calcium, and ammonium ions ($^{+}N(R)_3R'$, where R and R' independently designates optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl, optionally substituted aryl, or optionally substituted heteroaryl). Pharmaceutically acceptable salts are, e.g., those described in Remington's Pharmaceutical Sciences, 17. Ed. Alfonso R. Gennaro (Ed.), Mack Publishing Company, Easton, PA, U.S.A., 1985 and more recent editions and in Encyclopedia of Pharmaceutical Technology. Thus, the term "an acid addition salt or a basic salt thereof" used herein is intended to comprise such salts. Furthermore, the compounds as well as any intermediates or starting materials may also be present in hydrate form.

Embodiments

The function of V^1, V^2, V^3, and V^4 is mainly believed to be of sterical character, i.e. determinative for the orientation of the groups R^1-R^4. It is, however, also believed that the selection of a heteroatom as one or more of V^1, V^2, V^3, and V^4 may create dipole interactions with other entities and thereby ~~have~~has influence on, e.g., the solubility of the compounds of the general formula (I).

V^1, V^2, V^3, and V^4 are independently selected from a carbon atom, a non-quaternary nitrogen atom, an oxygen atom, and a sulfur atom, and ~~where~~ V^4 further may be selected from a bond, so that $-V^1-V^2-V^3-V^4-$ together with the atoms to which V^1 and V^4 are attached form an aromatic or heteroaromatic ring. Particularly useful examples of such aromatic rings and heteroaromatic rings are those selected from a benzene ring, a thiophene ring (V^1=S, V^2=V^3=C(-) and V^4=bond; V^2=S, V^1=V^3=C(-) and V^4=bond; or V^3=S, V^1=V^2=C(-) and V^4=bond), a furan ring (V^1=O, V^2=V^3=C(-) and V^4=bond; V^2=O, V^1=V^3=C(-) and V^4=bond; or V^3=O, V^1=V^2=C(-) and V^4=bond), a pyrazole ring (V^1=N(-), V^2=N, V^3=C(-) and V^4=bond; V^1=N, V^2=N(-), V^3=C(-) and V^4=bond), an imidazole ring (V^1=N(-), V^2=C(-), V^3=N and V^4=bond; V^1=N, V^2=C(-), V^3=N(-) and V^4=bond), a pyridine ring (V^1=N, V^2=V^3=V^4=C(-); V^2=N, V^1=V^3=V^4=C(-); V^3=N, V^1=V^2=V^4=C(-) and V^4=N, V^1=V^2=V^3=C(-)), a pyrimidine ring (V^1=V^3=N, V^2=V^4=C(-); V^2=V^4=N, V^1=V^3=C(-)), pyrazines (V^1=V^4=N, V^2=V^3=C(-)), a pyridazine ring (V^1=V^2=N, V^3=V^4=C(-); V^2=V^3=N, V^1=V^4=C(-); V^3=V^4=N, V^1=V^2=C(-)), a thiazole ring (V^1=N, V^2=C(-), V^3=S, V^4=bond; V^1=S, V^2=C(-), V^3=N, V^4=bond), and an isothiazole ring (V^1=N, V^2=S, V^3=C(-), V^4=bond; V^1=S, V^2=N, V^3=C(-), V^4=bond; V^1=C(-), V^2=S, V^3=N, V^4=bond; V^1=C(-), V^2=N, V^3=S, V^4=bond).

The meaning of V^1, V^2, V^3 and V^4 for each heteroaromatic ring is merely specified for the purpose of illustrating that various orientations of the heteroatoms are possible. Furthermore, it should be understood that the respective rings carry the substituents R^1, R^2, R^3 and R^4 (where applicable) in accordance with the general formula (I). Thus, specification of "C(-)" and "N(-)" as possible meanings of V^1, V^2, V^3 and V^4 is made for the purpose of describing that the atoms in question carry a substituent (which may be hydrogen). Specification of "N" means that the respective atoms do not carry an "R" substituent, i.e. the corresponding "R" substituent is absent.

In one embodiment, $-V^1-V^2-V^3-V^4-$ together with the atoms to which V^1 and V^4 are attached form a ring selected from a benzene ring, a thiophene ring, a furan ring, a pyrazole ring, an imidazole ring, a pyridine ring, a pyrimidine ring, pyrazines, and a pyridazine ring, in particular from a benzene ring and a pyridine ring where the nitrogen atom represents V^3 (see also the Examples). In accordance with the general formula (I), the respective ring (aromatic or heteroaromatic) carries the substituents R^1-R^4 (where applicable).

The substituents R^1-R^4 (where applicable) are believed to be at least partly responsible for the biological effect, e.g. the ability of the compounds to inhibit cell proliferation in cancer cells.

In one embodiment, R^1, R^2, R^3, and R^4 are, when attached to a carbon atom, independently selected from hydrogen, optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl,

hydroxy, optionally substituted C_{1-6}-alkoxy, optionally substituted C_{2-6}-alkenyloxy, carboxy, optionally substituted C_{1-6}-alkoxycarbonyl, optionally substituted C_{1-6}-alkylcarbonyl, optionally substituted C_{1-6}-alkylcarbonyloxy, formyl, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylsulphonylamino, cyano, carbamido, mono- and di(C_{1-6}-alkyl)aminocarbonylamino, C_{1-6}-alkanoyloxy, C_{1-6}-alkylsulphonyl, C_{1-6}-alkylsulphinyl, aminosulfonyl, mono- and di(C_{1-6}-alkyl)aminosulfonyl, nitro, optionally substituted C_{1-6}-alkylthio, and halogen, where any C_{1-6}-alkyl as an amino substituent is optionally substituted with hydroxy, C_{1-6}-alkoxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylaminocarbonyl, or halogen(s); and R^1, R^2, R^3, and R^4 are, when attached to a nitrogen atom, independently selected from hydrogen, optionally substituted C_{1-6}-alkyl, hydroxy, optionally substituted C_{1-6}-alkoxy, optionally substituted C_{1-6}-alkoxycarbonyl, optionally substituted C_{1-6}-alkylcarbonyl, formyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino, C_{1-6}-alkylcarbonylamino, mono- and di(C_{1-6}-alkyl)amino, C_{1-6}-alkylsulphonyl, and C_{1-6}-alkylsulphinyl; where any C_{1-6}-alkyl as an amino substituent is optionally substituted with hydroxy, C_{1-6}-alkoxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylaminocarbonyl, or halogen(s), and wherein any aryl, heterocyclyl and heteroaryl may be optionally substituted.

More particularly, R^1, R^2, R^3, and R^4 are independently selected from hydrogen, halogen, optionally substituted C_{1-6}-alkyl, hydroxy, optionally substituted C_{1-6}-alkoxy, optionally substituted C_{1-6}-alkoxycarbonyl, optionally substituted C_{1-6}-alkylcarbonyl, amino, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylsulphonylamino, mono- and di(C_{1-6}-alkyl)aminosulfonyl, and mono- and di(C_{1-6}-alkyl)amino, where any C_{1-6}-alkyl as an amino substituent is optionally substituted with hydroxy, C_{1-6}-alkoxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylaminocarbonyl, or halogen(s), such as from hydrogen, optionally substituted C_{1-6}-alkyl, hydroxy, optionally substituted C_{1-6}-alkoxy, optionally substituted C_{1-6}-alkoxycarbonyl, optionally substituted C_{1-6}-alkylcarbonyl, amino, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylsulphonylamino, mono- and di(C_{1-6}-alkyl)aminosulfonyl, and mono- and di(C_{1-6}-alkyl)amino, where any C_{1-6}-alkyl as an amino substituent is optionally substituted with hydroxy, C_{1-6}-alkoxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylaminocarbonyl, or halogen(s).

As an alternative to the above, R^1 and R^2 may in one embodiment together with the carbon atoms to which they are attached form a heterocyclic ring or a heteroaromatic ring; and in another embodiment, R^1 and R^2 may together with the carbon atoms to which they are attached form an aromatic ring or a carbocyclic ring.

In one particular variant, R^1 is selected from hydrogen, halogen, C_{1-6}-alkyl, trifluoromethyl and C_{1-6}-alkoxy, when V^1 is a carbon atom.

In a further variant, R^2 is selected from hydrogen, halogen, optionally substituted aryl, optionally substituted aryloxy, and optionally substituted heteroaryl, when V^2 is a carbon atom.

In a still further variant, R^3 is selected from hydrogen, optionally substituted C_{1-6}-alkoxy, halogen, cyano, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heteroaryl, amino, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylsulphonylamino, and mono- and di(C_{1-6}-alkyl)aminosulfonyl, when V^3 is a carbon atom.

In an even still further variant, R^4 is hydrogen, when V^4 is a carbon atom.

According to the principal embodiment of the invention, it is believed that the substituents X^1 and X^2 must include a heteroatom directly bound to the phenyl ring, cf. the definition further above. (See also the alternative embodiment described further below.)

In one embodiment, X^1 and X^2 are independently selected from hydroxy, optionally substituted C_{1-6}-alkoxy, optionally substituted C_{1-6}-alkylcarbonyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylsulphonylamino, mono- and di(C_{1-6}-alkyl)aminocarbonylamino, C_{1-6}-alkanoyloxy, and mono- and di(C_{1-6}-alkyl)aminosulfonyl, where any C_{1-6}-alkyl as an amino substituent is optionally substituted with hydroxy, C_{1-6}-alkoxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylaminocarbonyl, or halogen(s).

In a more preferred embodiment, X^1 and X^2 independently are selected from halogen, OR^6, $OCOR^5$, $N(R^6)_2$, $NHCOR^5$, $NHSO_2R^5$, and $NHCON(R^6)_2$, wherein R^5 is selected from C_{1-6}-alkyl, optionally substituted aryl and optionally substituted heteroaryl, and each R^6 independently is selected from hydrogen, C_{1-6}-alkyl, optionally substituted aryl and optionally substituted heteroaryl, such as from OR^6, $OCOR^5$, $N(R^6)_2$, $NHCOR^5$, $NHSO_2R^5$, and $NHCON(R^6)_2$, wherein R^5 is selected from C_{1-6}-alkyl, optionally substituted aryl and optionally substituted heteroaryl, and each R^6 independently is selected from hydrogen, C_{1-6}-alkyl, optionally substituted aryl and optionally substituted heteroaryl, in particular X^1 and X^2 are independently selected from halogen, hydroxy, OAc, NH_2, NMe_2, NHAc, $NHSO_2Me$ and $NHCONMe_2$, such as from hydroxy, OAc, NH_2, NMe_2, NHAc, $NHSO_2Me$ and $NHCONMe_2$.

This being said, it is currently believed that X^1 and X^2 may be the same for both phenyl rings, i.e. $X^1=X^2$. This has the advantage that achiral compounds are achieved. In the pharmaceutical business, use of chiral drugs typically requires isolation of the individual stereoisomeric forms. Another advantage is seen in the synthesis route. A one-step

introduction of the two PhX groups saves at least one synthesis step and associated time, and increases the overall yield of the preparation process.

Although not explicitly specified in the general formula (I), it is believed that introduction of fluoro atoms in the benzene rings may provide certain advantages. Thus, as defined above, a variant of compounds ~~are~~includes those wherein each of the benzene rings to which X^1 and X^2 are attached further may be substituted with one, two, three or four fluoro atoms, in particular each benzene ring to which X^1 and X^2 are attached ~~are~~is substituted with two fluoro atoms in the ortho positions relative to the substituents X^1 and X^2, respectively.

The structural element $>Y(=Q)_n$ is not considered particularly critical. However, for synthetic reasons, it is preferred that Y is a carbon atom and Q is an oxygen atom, i.e. $>Y(=Q)_n$ is $>C=O$. In the alternative, Y is a sulfur atom, n is 2, and each Q is an oxygen atom, i.e. $>Y(=Q)_n$ is $>S(=O)_2$.

It is believed that R^N may be selected from a wide variety of substituents. However, it is currently believed that it may be advantageous if R^N is selected from hydrogen, C_{1-6}-alkyl, amino, and C_{1-6}-alkylcarbonylamino. Most preferred ~~is~~are the embodiments wherein R^N is hydrogen (see Figure 1).

In view of the above, and in view of the current set of biological data, it is postulated that certain subclasses of compounds may exhibit particular advantages, cf. the subclasses defined in the following:

(a) One subclass of compounds are those wherein V^1, V^2, V^3, V^4 all are a carbon atom, $>Y(=Q)_n$ is $>C=O$, and R^N is hydrogen.

In a first embodiment hereof, R^4 is hydrogen; in particular, both of R^3 and R^4 are hydrogen.

In a second embodiment within the subclass, which may be combined with the first embodiment, R^1 is C_{1-4}-alkyl and R^2 is halogen, e.g. R^1 is methyl and R^2 is chloro.

In a third embodiment within this subclass, which may be combined with the first embodiment, R^1 and R^2 together with the carbon atoms to which they are attached form a ring, e.g. an aromatic ring, a carbocyclic ring, a heterocyclic ring or a heteroaromatic ring, in particular an aromatic ring or a carbocyclic ring.

In a fourth embodiment within this subclass, which may be combined with the preceding embodiments, each of X^1 and X^2 independently ~~are~~is selected from halogen, hydroxy, C_{1-4}-alkoxy, amino, and dimethylamino.

In a fifth embodiment within this subclass, which may be combined with the first embodiment, R^1, R^2 and R^4 all are hydrogen.

In a sixth embodiment within this subclass, which may be combined with the fifth embodiment, R^3 is selected from hydrogen, halogen (such as fluoro, chloro, bromo, iodo), nitro, C_{1-4}-alkyl (such as methyl), C_{1-4}-alkoxy (such as methoxy), trifluoromethoxy, amino, carboxy, and dimethylaminocarbonyl, in particular hydrogen, halogen (such as fluoro, chloro, bromo, iodo), nitro, methyl, methoxy, and amino.

In a seventh embodiment within this subclass, which is combined with the fifth or sixth embodiment, each of X^1 and X^2 independently ~~are~~is selected from halogen, hydroxy, C_{1-4}-alkoxy, amino, and dimethylamino.

In an eighth embodiment within this subclass, R^2, R^3 and R^4 all are hydrogen.

In a ninth embodiment within this subclass, which may be combined with the eighth embodiment, R^1 is selected from fluoro, chloro, bromo, C_{1-4}-alkyl (such as methyl or tert-butyl), trifluoromethyl, C_{1-4}-alkoxy (such as methoxy), and dimethylaminocarbonyl.

In a tenth embodiment, which may be combined with any of the eighth and ninth embodiments, each of X^1 and X^2 independently ~~are~~is selected from halogen (such as fluoro) hydroxy, C_{1-4}-alkoxy (such as methoxy), amino, and dimethylamino.

In an eleventh embodiment series, which may be combined with the first embodiment, R^1 is selected from halogen (such as fluoro, chloro, bromo), C_{1-4}-alkyl (such as methyl or tert-butyl), trifluoromethyl, C_{1-4}-alkoxy (such as methoxy), and dimethylaminocarbonyl, R^2 is selected from hydrogen and halogen, and R^3 is selected from hydrogen, halogen, C_{1-4}-alkyl (such as methyl), and amino; where R^2 and R^3 are not both hydrogen.

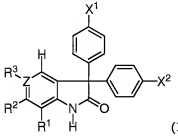
Also preferred within this subclass and any of the embodiments are the variants, wherein X^1 and X^2 are the same.

(b) Another subclass of compounds are those wherein at least one of V^1, V^2, V^3, and V^4 is selected from a non-quaternary nitrogen atom, an oxygen atom, and a sulfur atom, and

where V^4 further may be selected from a bond, so that $-V^1-V^2-V^3-V^4-$ together with the atoms to which V^1 and V^4 are attached form a heteroaromatic ring. In this case, the heteroaromatic ring is preferably selected from a pyridine ring and a pyrazole ring.

Within this subclass, it is further preferred that $>Y(=Q)_n$ is $>C=O$ and R^N is hydrogen. Also preferred are the embodiments, wherein X^1 and X^2 are the same.

A further aspect of the invention relates to the use of a 3,3-diphenyl-1,3-dihydro-indol-2-one type compound of the formula (IIa)



(IIa)

wherein

R^1 is selected from hydrogen, halogen, C_{1-6}-alkyl, trifluoromethyl and C_{1-6}-alkoxy;

R^2 is selected from hydrogen, halogen, optionally substituted aryl, optionally substituted aryloxy, and optionally substituted heteroaryl;

R^3 is selected from hydrogen, optionally substituted C_{1-6}-alkoxy, halogen, cyano, and optionally substituted aryl, optionally substituted aryloxy, optionally substituted heteroaryl, amino, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylsulphonylamino, and mono- and di(C_{1-6}-alkyl)aminosulfonyl;

Z is CH or N; and

X^1 and X^2 are independently selected from halogen, OR^6, $OCOR^5$, $N(R^6)_2$, $NHCOR^5$, $NHSO_2R^5$, and $NHCON(R^6)_2$, wherein R^5 is selected from C_{1-6}-alkyl, optionally substituted aryl and optionally substituted heteroaryl, and each R^6 independently is selected from hydrogen, C_{1-6}-alkyl, optionally substituted aryl and optionally substituted heteroaryl; and

pharmaceutically acceptable salts and prodrugs thereof (as defined further above);

for the preparation of a medicament for the treatment of cancer in a mammal.

As above, each of the benzene rings to which X^1 and X^2 are attached further may be substituted with one, two, three or four fluoro atoms, in particular each benzene ring to which X^1 and X^2 are attached ~~are~~is substituted with two fluoro atoms in the ortho positions relative to the substituents X^1 and X^2, respectively.

In one embodiment, X^1 and X^2 are independently selected from OR^6, $OCOR^5$, $N(R^6)_2$, $NHCOR^5$, $NHSO_2R^5$, and $NHCON(R^6)_2$, wherein R^5 is selected from C_{1-6}-alkyl, optionally substituted aryl and optionally substituted heteroaryl, and each R^6 independently is selected from hydrogen, C_{1-6}-alkyl, optionally substituted aryl and optionally substituted heteroaryl.

In one variant which may be combined with the before-mentioned embodiments within this aspect, R^1 is selected from C_{1-6}-alkyl and C_{1-6}-alkoxy, such as from methyl, ethyl, isopropyl, methoxy, ethoxy and isopropoxy, in particular from methoxy, ethoxy and isopropoxy, or from methyl, ethyl, and isopropyl.

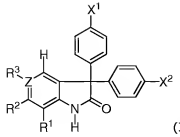
In another variant which may be combined with the before-mentioned embodiments and variants within this aspect, R^2 is selected from hydrogen, chloro, methoxy, dimethylamino, phenyl, phenoxy, optionally substituted thiophen-2-yl, and optionally substituted thiophen-3-yl.

In still another variant which may be combined with the before-mentioned embodiments and variants within this aspect, R^3 is selected from hydrogen, methoxy, fluoro, chloro, cyano, phenyl, phenoxy, optionally substituted thiophen-2-yl, and optionally substituted thiophen-3-yl, amino, acetylamino, methylsulfonylamino, and dimethylaminosulfonyl.

In a still further variant, X^1 and X^2 independently are selected from halogen, hydroxy, OAc, NH_2, NMe_2, NHAc, $NHSO_2Me$ and $NHCONMe_2$, such as from hydroxy, OAc, NH_2, NMe_2, NHAc, $NHSO_2Me$ and $NHCONMe_2$.

Within this aspect, each X^1 and X^2 are preferably the same.

A still further aspect of the invention relates to the use of a 3,3-diphenyl-1,3-dihydro-indol-2-one type compound of the formula (IIb)



(IIb)

wherein

R^1, R^2, and R^3, when attached to a carbon atom, independently are selected from hydrogen, optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl, hydroxy, optionally substituted C_{1-6}-alkoxy, optionally substituted C_{2-6}-alkenyloxy, carboxy, optionally substituted C_{1-6}-alkoxycarbonyl, optionally substituted C_{1-6}-alkylcarbonyl, optionally substituted C_{1-6}-alkylcarbonyloxy, formyl, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylsulphonylamino, cyano, carbamido, mono- and di(C_{1-6}-alkyl)aminocarbonylamino, C_{1-6}-alkanoyloxy, C_{1-6}-alkylsulphonyl, C_{1-6}-alkylsulphinyl, aminosulfonyl, mono- and di(C_{1-6}-alkyl)aminosulfonyl, nitro, optionally substituted C_{1-6}-alkylthio, and halogen, where any C_{1-6}-alkyl as an amino substituent is optionally substituted with hydroxy, C_{1-6}-alkoxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylaminocarbonyl, or halogen(s); and

R^1, R^2, and R^3, when attached to a nitrogen atom, independently are selected from hydrogen, optionally substituted C_{1-6}-alkyl, hydroxy, optionally substituted C_{1-6}-alkoxy, optionally substituted C_{1-6}-alkoxycarbonyl, optionally substituted C_{1-6}-alkylcarbonyl, formyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino, C_{1-6}-alkylcarbonylamino, mono- and di(C_{1-6}-alkyl)amino, C_{1-6}-alkylsulphonyl, and C_{1-6}-alkylsulphinyl; where any C_{1-6}-alkyl as an amino substituent is optionally substituted with hydroxy, C_{1-6}-alkoxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylaminocarbonyl, or halogen(s), and wherein any aryl, heterocyclyl and heteroaryl may be optionally substituted;

or wherein R^1 and R^2 together with the carbon and/or nitrogen atoms to which they are attached form a heterocyclic ring, a heteroaromatic ring, an aromatic ring or a carbocyclic ring;

Z is CH or N; and

X^1 and X^2 are independently selected from halogen, OR^6, $OCOR^5$, $N(R^6)_2$, $NHCOR^5$, $NHSO_2R^5$, and $NHCON(R^6)_2$, wherein R^5 is selected from C_{1-6}-alkyl, optionally substituted aryl and

optionally substituted heteroaryl, and each R^6 independently is selected from hydrogen, C_{1-6}-alkyl, optionally substituted aryl and optionally substituted heteroaryl; and

pharmaceutically acceptable salts and prodrugs thereof;

for the preparation of a medicament for the treatment of cancer in a mammal.

In one embodiment, R^1, R^2, and R^3 independently are selected from hydrogen, halogen, optionally substituted C_{1-6}-alkyl, hydroxy, optionally substituted C_{1-6}-alkoxy, optionally substituted C_{1-6}-alkoxycarbonyl, optionally substituted C_{1-6}-alkylcarbonyl, amino, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylsulphonylamino, mono- and di(C_{1-6}-alkyl)aminosulfonyl, nitro, cyano, and mono- and di(C_{1-6}-alkyl)amino, where any C_{1-6}-alkyl as an amino substituent is optionally substituted with hydroxy, C_{1-6}-alkoxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylaminocarbonyl, or halogen(s); preferably, R^1, R^2, and R^3 independently are selected from hydrogen, optionally substituted C_{1-6}-alkyl, hydroxy, optionally substituted C_{1-6}-alkoxy, optionally substituted C_{1-6}-alkoxycarbonyl, optionally substituted C_{1-6}-alkylcarbonyl, amino, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylsulphonylamino, mono- and di(C_{1-6}-alkyl)aminosulfonyl, nitro, cyano, and mono- and di(C_{1-6}-alkyl)amino, where any C_{1-6}-alkyl as an amino substituent is optionally substituted with hydroxy, C_{1-6}-alkoxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylaminocarbonyl, or halogen(s).

~~An~~In another embodiment, R^1 and R^2 together with the carbon atoms to which they are attached form a heterocyclic ring or a heteroaromatic ring.

In still another embodiment, R^1 and R^2 together with the carbon atoms to which they are attached form an aromatic ring or a carbocyclic ring.

In preferred variants of the above aspect and embodiments, Z is CH.

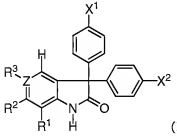
In further preferred variants of the above aspect, embodiments and variant, X^1 and X^2 are independently selected from halogen, OR^6, $OCOR^5$, $N(R^6)_2$, $NHCOR^5$, $NHSO_2R^5$, and $NHCON(R^6)_2$, wherein R^5 is selected from C_{1-6}-alkyl, optionally substituted aryl and optionally substituted heteroaryl, and each R^6 independently is selected from hydrogen, C_{1-6}-alkyl, optionally substituted aryl and optionally substituted heteroaryl; in particular X^1 and X^2 are independently selected from halogen, OR^6, and $OCOR^5$, wherein R^5 is selected from C_{1-6}-alkyl, optionally substituted aryl and optionally substituted heteroaryl, and each R^6 independently is selected from hydrogen, C_{1-6}-alkyl, optionally substituted aryl and optionally substituted heteroaryl.

In further preferred variants of the above aspect, embodiments and variants, R^1 and R^2 independently are selected from hydrogen, halogen, C_{1-6}-alkyl, cyano, trifluoromethyl and C_{1-6}-alkoxy; R^3 is selected from hydrogen, C_{1-6}-alkoxy, halogen, nitro, cyano, and amino.

Alternative embodiments

An alternative subclass of ~~compound~~compounds applicable for the use defined hereinabove, is essentially as defined above for the compounds of Formula I, but with the modification that X^1 and X^2 are not the same. In a main embodiment hereof, one of X^1 and X^2 is as defined for X^1 and X^2 above, whereas the other of X^1 and X^2 is a carbon-substituent, e.g. a substituent selected from optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl, carboxy, optionally substituted C_{1-6}-alkoxycarbonyl, optionally substituted C_{1-6}-alkylcarbonyl, formyl, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, cyano, aryl, arylcarbonyl, heterocyclyl, heterocyclylcarbonyl, heteroaryl, heteroarylcarbonyl, where any C_{1-6}-alkyl as an amino substituent is optionally substituted with hydroxy, C_{1-6}-alkoxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylaminocarbonyl, or halogen(s), and wherein any aryl, heterocyclyl and heteroaryl may be optionally substituted. The remaining substituents are as defined above.

Thus, a further aspect of the invention relates to the use of a 3,3-diphenyl-1,3-dihydro-indol-2-one type compound of the formula (IIc)



(IIc)

wherein

R^1 is selected from hydrogen, halogen, C_{1-6}-alkyl, trifluoromethyl and C_{1-6}-alkoxy;

R^2 is selected from hydrogen, halogen, optionally substituted aryl, optionally substituted aryloxy, and optionally substituted heteroaryl;

R^3 is selected from hydrogen, optionally substituted C_{1-6}-alkoxy, halogen, cyano, and optionally substituted aryl, optionally substituted aryloxy, optionally substituted heteroaryl,

amino, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylsulphonylamino, and mono- and di(C_{1-6}-alkyl)aminosulfonyl;

Z is CH or N; and

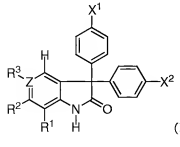
one of X^1 and X^2 is selected from halogen, OR^6, $OCOR^5$, $N(R^6)_2$, $NHCOR^5$, $NHSO_2R^5$, and $NHCON(R^6)_2$, wherein R^5 is selected from C_{1-6}-alkyl, optionally substituted aryl and optionally substituted heteroaryl, and each R^6 independently is selected from hydrogen, C_{1-6}-alkyl, optionally substituted aryl and optionally substituted heteroaryl; and the other of X^1 and X^2 is selected from optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl, carboxy, optionally substituted C_{1-6}-alkoxycarbonyl, optionally substituted C_{1-6}-alkylcarbonyl, formyl, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, cyano, aryl, arylcarbonyl, heterocyclyl, heterocyclylcarbonyl, heteroaryl, heteroarylcarbonyl, where any C_{1-6}-alkyl as an amino substituent is optionally substituted with hydroxy, C_{1-6}-alkoxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylaminocarbonyl, or halogen(s), and wherein any aryl, heterocyclyl and heteroaryl may be optionally substituted; and

pharmaceutically acceptable salts and prodrugs thereof (as defined further above);

for the preparation of a medicament for the treatment of cancer in a mammal.

The embodiments defined for the compound (IIa) above also apply for the compound of the Formula (IIc), *mutatis mutantis*.

A still further aspect of the invention relates to the use of a 3,3-diphenyl-1,3-dihydro-indol-2-one type compound of the formula (IId)



(IId)

wherein

R^1, R^2, and R^3, when attached to a carbon atom, independently are selected from hydrogen, optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl, hydroxy, optionally

substituted C_{1-6}-alkoxy, optionally substituted C_{2-6}-alkenyloxy, carboxy, optionally substituted C_{1-6}-alkoxycarbonyl, optionally substituted C_{1-6}-alkylcarbonyl, optionally substituted C_{1-6}-alkylcarbonyloxy, formyl, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylsulphonylamino, cyano, carbamido, mono- and di(C_{1-6}-alkyl)aminocarbonylamino, C_{1-6}-alkanoyloxy, C_{1-6}-alkylsulphonyl, C_{1-6}-alkylsulphinyl, aminosulfonyl, mono- and di(C_{1-6}-alkyl)aminosulfonyl, nitro, optionally substituted C_{1-6}-alkylthio, and halogen, where any C_{1-6}-alkyl as an amino substituent is optionally substituted with hydroxy, C_{1-6}-alkoxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylaminocarbonyl, or halogen(s); and

R^1, R^2, and R^3, when attached to a nitrogen atom, independently are selected from hydrogen, optionally substituted C_{1-6}-alkyl, hydroxy, optionally substituted C_{1-6}-alkoxy, optionally substituted C_{1-6}-alkoxycarbonyl, optionally substituted C_{1-6}-alkylcarbonyl, formyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino, C_{1-6}-alkylcarbonylamino, mono- and di(C_{1-6}-alkyl)amino, C_{1-6}-alkylsulphonyl, and C_{1-6}-alkylsulphinyl; where any C_{1-6}-alkyl as an amino substituent is optionally substituted with hydroxy, C_{1-6}-alkoxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylaminocarbonyl, or halogen(s), and wherein any aryl, heterocyclyl and heteroaryl may be optionally substituted;

or wherein R^1 and R^2 together with the carbon and/or nitrogen atoms to which they are attached form a heterocyclic ring, a heteroaromatic ring, an aromatic ring or a carbocyclic ring;

Z is CH or N; and

one of X^1 and X^2 is selected from halogen, OR^6, $OCOR^5$, $N(R^6)_2$, $NHCOR^5$, $NHSO_2R^5$, and $NHCON(R^6)_2$, wherein R^5 is selected from C_{1-6}-alkyl, optionally substituted aryl and optionally substituted heteroaryl, and each R^6 independently is selected from hydrogen, C_{1-6}-alkyl, optionally substituted aryl and optionally substituted heteroaryl; and the other of X^1 and X^2 is selected from optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl, carboxy, optionally substituted C_{1-6}-alkoxycarbonyl, optionally substituted C_{1-6}-alkylcarbonyl, formyl, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, cyano, aryl, arylcarbonyl, heterocyclyl, heterocyclylcarbonyl, heteroaryl, heteroarylcarbonyl, where any C_{1-6}-alkyl as an amino substituent is optionally substituted with hydroxy, C_{1-6}-alkoxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylaminocarbonyl, or halogen(s), and wherein any aryl, heterocyclyl and heteroaryl may be optionally substituted; and

pharmaceutically acceptable salts and prodrugs thereof;

for the preparation of a medicament for the treatment of cancer in a mammal.

The embodiments defined for the compound (IIb) above also apply for the compound of the Formula (IId), *mutatis mutantis*.

Presently very interesting compounds of the formula I are those listed in the following as Items 1 to 225:

1 5-Amino-6-chloro-3,3-bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-indol-2-one
2 5-Chloro-3,3-bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-indol-2-one
3 5-Fluoro-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one
4 3,3-Bis-(4-hydroxy-phenyl)-5-nitro-1,3-dihydro-indol-2-one
5 3,3-Bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one
6 6-Bromo-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one
7 6-Bromo-3,3-bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one
8 6-Bromo-3,3-bis-(4-hydroxy-phenyl)-5,7-dimethyl-1,3-dihydro-indol-2-one
9 6-Bromo-3,3-bis-(4-hydroxy-phenyl)-7-methyl-2-oxo-2,3-dihydro-1H-indole-5-carbonitrile
10 6-Bromo-3,3-bis-(4-hydroxy-phenyl)-5-methoxy-7-methyl-1,3-dihydro-indol-2-one
11 6-Bromo-3,3-bis-(4-hydroxy-phenyl)-7-methoxy-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one;
12 6-Bromo-7-ethyl-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one
13 6-Bromo-7-ethyl-3,3-bis-(4-hydroxy-phenyl)-5-methyl-1,3-dihydro-indol-2-one
14 6-Bromo-5-ethyl-3,3-bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-indol-2-one
15 6-Bromo-7-ethyl-3,3-bis-(4-hydroxy-phenyl)-2-oxo-2,3-dihydro-1H-indole-5-carbonitrile
16 6-Bromo-7-ethyl-3,3-bis-(4-hydroxy-phenyl)-5-methoxy-1,3-dihydro-indol-2-one
17 6-Chloro-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one
18 6-Chloro-3,3-bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one
19 6-Chloro-3,3-bis-(4-hydroxy-phenyl)-5,7-dimethyl-1,3-dihydro-indol-2-one
20 6-Chloro-3,3-bis-(4-hydroxy-phenyl)-7-methyl-2-oxo-2,3-dihydro-1H-indole-5-carbonitrile
21 6-Chloro-3,3-bis-(4-hydroxy-phenyl)-5-methoxy-7-methyl-1,3-dihydro-indol-2-one
22 6-Chloro-3,3-bis-(4-hydroxy-phenyl)-7-methoxy-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one
23 6-Chloro-7-ethyl-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one
24 6-Chloro-7-ethyl-3,3-bis-(4-hydroxy-phenyl)-5-methyl-1,3-dihydro-indol-2-one
25 6-Chloro-5-ethyl-3,3-bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-indol-2-one
26 6-Chloro-7-ethyl-3,3-bis-(4-hydroxy-phenyl)-2-oxo-2,3-dihydro-1H-indole-5-carbonitrile
27 6-Chloro-7-ethyl-3,3-bis-(4-hydroxy-phenyl)-5-methoxy-1,3-dihydro-indol-2-one
28 6-Chloro-3,3-bis-(4-hydroxy-phenyl)-5-methyl-7-methoxy-1,3-dihydro-indol-2-one;
29 6-Chloro-3,3-bis-(4-hydroxy-phenyl)-7-methoxy-2-oxo-2,3-dihydro-1H-indole-5-carbonitrile;
30 6-Chloro-3,3-bis-(4-hydroxy-phenyl)-7-methoxy-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one;
31 6-Chloro-3,3-bis-(4-hydroxy-phenyl)-7-methoxy-5-methyl-1,3-dihydro-indol-2-one;
32 6-Chloro-5-ethyl-3,3-bis-(4-hydroxy-phenyl)-7-methoxy-1,3-dihydro-indol-2-one;
33 6-Chloro-3,3-bis-(4-hydroxy-phenyl)-5,7-dimethoxy-1,3-dihydro-indol-2-one;
34 N-{4-[3-(4-Acetylamino-phenyl)-5-chloro-7-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-phenyl}-acetamide;
35 N-{4-[5-Chloro-3-(4-methanesulfonylamino-phenyl)-7-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-phenyl}-methanesulfonamide
36 N-{4-[3-(4-Acetylamino-phenyl)-6-chloro-7-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-phenyl}-acetamide;
37 N-{4-[6-Chloro-3-(4-methanesulfonylamino-phenyl)-7-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-phenyl}-methanesulfonamide;
38 N-{4-[3-(4-Acetylamino-phenyl)-5-chloro-7-methoxy-2-oxo-2,3-dihydro-1H-indol-3-yl]-phenyl}-acetamide;
39 N-{4-[5-Chloro-3-(4-methanesulfonylamino-phenyl)-7-methoxy-2-oxo-2,3-dihydro-1H-indol-3-yl]-phenyl}-methanesulfonamide;
40 N-{4-[3-(4-Acetylamino-phenyl)-6-chloro-7-methoxy-2-oxo-2,3-dihydro-1H-indol-3-yl]-phenyl}-acetamide; and
41 N-{4-[6-Chloro-3-(4-methanesulfonylamino-phenyl)-7-methoxy-2-oxo-2,3-dihydro-1H-indol-3-yl]-phenyl}-methanesulfonamide
42 2-Chloro-6,6-bis-(4-hydroxy-phenyl)-3-methyl-4,6-dihydro-3H-pyrrolo[2,3-d]imidazol-5-one

43 Acetic acid 4-[6-(4-acetoxy-phenyl)-2-chloro-3-methyl-5-oxo-3,4,5,6-tetrahydro-pyrrolo[2,3-d]imidazol-6-yl]-phenyl ester
44 6,6-Bis-(4-amino-phenyl)-2-chloro-3-methyl-4,6-dihydro-3H-pyrrolo[2,3-d]imidazol-5-one
45 2-Chloro-6,6-bis-(4-dimethylamino-phenyl)-3-methyl-4,6-dihydro-3H-pyrrolo[2,3-d]imidazol-5-one
46 N-{4-[6-(4-Acetylamino-phenyl)-2-chloro-3-methyl-5-oxo-3,4,5,6-tetrahydro-pyrrolo[2,3-d]imidazol-6-yl]-phenyl}-acetamide
47 N-{4-[2-Chloro-6-(4-methanesulfonylamino-phenyl)-3-methyl-5-oxo-3,4,5,6-tetrahydro-pyrrolo[2,3-d]imidazol-6-yl]-phenyl}-methanesulfonamide
48 4,4-Bis-(4-hydroxy-phenyl)-1-methyl-4,6-dihydro-1H-pyrrolo[2,3-c]pyrazol-5-one
49 Acetic acid 4-[4-(4-acetoxy-phenyl)-1-methyl-5-oxo-1,4,5,6-tetrahydro-pyrrolo[2,3-c]pyrazol-4-yl]-phenyl ester
50 4,4-Bis-(4-amino-phenyl)-1-methyl-4,6-dihydro-1H-pyrrolo[2,3-c]pyrazol-5-one
51 N-{4-[4-(4-Methanesulfonylamino-phenyl)-1-methyl-5-oxo-1,4,5,6-tetrahydro-pyrrolo[2,3-c]pyrazol-4-yl]-phenyl}-methanesulfonamide
52 4,4-Bis-(4-dimethylamino-phenyl)-1-methyl-4,6-dihydro-1H-pyrrolo[2,3-c]pyrazol-5-one
53 N-{4-[4-(4-Acetylamino-phenyl)-1-methyl-5-oxo-1,4,5,6-tetrahydro-pyrrolo[2,3-c]pyrazol-4-yl]-phenyl}-acetamide
54 4,4-Bis-(4-hydroxy-phenyl)-2-methyl-2,6-dihydro-4H-pyrrolo[2,3-c]pyrazol-5-one
55 Acetic acid 4-[4-(4-acetoxy-phenyl)-2-methyl-5-oxo-2,4,5,6-tetrahydro-pyrrolo[2,3-c]pyrazol-4-yl]-phenyl ester
56 4,4-Bis-(4-amino-phenyl)-2-methyl-2,6-dihydro-4H-pyrrolo[2,3-c]pyrazol-5-one
57 4,4-Bis-(4-dimethylamino-phenyl)-2-methyl-2,6-dihydro-4H-pyrrolo[2,3-c]pyrazol-5-one
58 N-{4-[4-(4-Acetylamino-phenyl)-2-methyl-5-oxo-2,4,5,6-tetrahydro-pyrrolo[2,3-c]pyrazol-4-yl]-phenyl}-acetamide
59 N-{4-[4-(4-Methanesulfonylamino-phenyl)-2-methyl-5-oxo-2,4,5,6-tetrahydro-pyrrolo[2,3-c]pyrazol-4-yl]-phenyl}-methanesulfonamide
60 4,4-Bis-(4-hydroxy-phenyl)-4,6-dihydro-thieno[2,3-b]pyrrol-5-one
61 Acetic acid 4-[4-(4-acetoxy-phenyl)-5-oxo-5,6-dihydro-4H-thieno[2,3-b]pyrrol-4-yl]-phenyl ester
62 4,4-Bis-(4-amino-phenyl)-4,6-dihydro-thieno[2,3-b]pyrrol-5-one
63 4,4-Bis-(4-dimethylamino-phenyl)-4,6-dihydro-thieno[2,3-b]pyrrol-5-one
64 N-{4-[4-(4-Acetylamino-phenyl)-5-oxo-5,6-dihydro-4H-thieno[2,3-b]pyrrol-4-yl]-phenyl}-acetamide
65 N-{4-[4-(4-Methanesulfonylamino-phenyl)-5-oxo-5,6-dihydro-4H-thieno[2,3-b]pyrrol-4-yl]-phenyl}-methanesulfonamide
66 2-Chloro-4,4-bis-(4-hydroxy-phenyl)-4,6-dihydro-thieno[2,3-b]pyrrol-5-one
67 Acetic acid 4-[4-(4-acetoxy-phenyl)-2-chloro-5-oxo-5,6-dihydro-4H-thieno[2,3-b]pyrrol-4-yl]-phenyl ester
68 4,4-Bis-(4-amino-phenyl)-2-chloro-4,6-dihydro-thieno[2,3-b]pyrrol-5-one
69 2-Chloro-4,4-bis-(4-dimethylamino-phenyl)-4,6-dihydro-thieno[2,3-b]pyrrol-5-one
70 N-{4-[4-(4-Acetylamino-phenyl)-2-chloro-5-oxo-5,6-dihydro-4H-thieno[2,3-b]pyrrol-4-yl]-phenyl}-acetamide
71 N-{4-[2-Chloro-4-(4-methanesulfonylamino-phenyl)-5-oxo-5,6-dihydro-4H-thieno[2,3-b]pyrrol-4-yl]-phenyl}-methanesulfonamide
72 4,4-Bis-(4-hydroxy-phenyl)-4,6-dihydro-furo[2,3-b]pyrrol-5-one
73 Acetic acid 4-[4-(4-acetoxy-phenyl)-5-oxo-5,6-dihydro-4H-furo[2,3-b]pyrrol-4-yl]-phenyl ester
74 4,4-Bis-(4-amino-phenyl)-4,6-dihydro-furo[2,3-b]pyrrol-5-one
75 4,4-Bis-(4-dimethylamino-phenyl)-4,6-dihydro-furo[2,3-b]pyrrol-5-one
76 N-{4-[4-(4-Acetylamino-phenyl)-5-oxo-5,6-dihydro-4H-furo[2,3-b]pyrrol-4-yl]-phenyl}-acetamide
77 N-{4-[4-(4-Methanesulfonylamino-phenyl)-5-oxo-5,6-dihydro-4H-furo[2,3-b]pyrrol-4-yl]-phenyl}-methanesulfonamide
78 2-Chloro-4,4-bis-(4-hydroxy-phenyl)-4,6-dihydro-furo[2,3-b]pyrrol-5-one
79 Acetic acid 4-[4-(4-acetoxy-phenyl)-2-chloro-5-oxo-5,6-dihydro-4H-furo[2,3-b]pyrrol-4-yl]-phenyl ester
80 4,4-Bis-(4-amino-phenyl)-2-chloro-4,6-dihydro-furo[2,3-b]pyrrol-5-one
81 2-Chloro-4,4-bis-(4-dimethylamino-phenyl)-4,6-dihydro-furo[2,3-b]pyrrol-5-one
82 N-{4-[4-(4-Acetylamino-phenyl)-2-chloro-5-oxo-5,6-dihydro-4H-furo[2,3-b]pyrrol-4-yl]-phenyl}-acetamide
83 N-{4-[2-Chloro-4-(4-methanesulfonylamino-phenyl)-5-oxo-5,6-dihydro-4H-furo[2,3-b]pyrrol-4-yl]-phenyl}-methanesulfonamide
84 3,3-Bis-(4-hydroxy-phenyl)-6-methyl-3,8-dihydro-1H-1,8-diaza-as-indacen-2-one
85 Acetic acid 4-[3-(4-acetoxy-phenyl)-6-methyl-2-oxo-1,2,3,8-tetrahydro-1,8-diaza-as-indacen-3-yl]-phenyl ester
86 3,3-Bis-(4-amino-phenyl)-6-methyl-3,8-dihydro-1H-1,8-diaza-as-indacen-2-one
87 3,3-Bis-(4-dimethylamino-phenyl)-6-methyl-3,8-dihydro-1H-1,8-diaza-as-indacen-2-one

88 N-{4-[3-(4-Acetylamino-phenyl)-6-methyl-2-oxo-1,2,3,8-tetrahydro-1,8-diaza-as-indacen-3-yl]-phenyl}-acetamide
89 N-{4-[3-(4-Methanesulfonylamino-phenyl)-6-methyl-2-oxo-1,2,3,8-tetrahydro-1,8-diaza-as-indacen-3-yl]-phenyl}-methanesulfonamide
90 3,3-Bis-(4-hydroxy-phenyl)-1,3-dihydro-benzo[g]indol-2-one
91 Acetic acid 4-[3-(4-acetoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[g]indol-3-yl]-phenyl ester
92 3,3-Bis-(4-amino-phenyl)-1,3-dihydro-benzo[g]indol-2-one
93 3,3-Bis-(4-dimethylamino-phenyl)-1,3-dihydro-benzo[g]indol-2-one
94 N-{4-[3-(4-Acetylamino-phenyl)-2-oxo-2,3-dihydro-1H-benzo[g]indol-3-yl]-phenyl}-acetamide
95 N-{4-[3-(4-Methanesulfonylamino-phenyl)-2-oxo-2,3-dihydro-1H-benzo[g]indol-3-yl]-phenyl}-methanesulfonamide
96 1-Amino-6-chloro-3,3-bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-indol-2-one
97 Acetic acid 4-[3-(4-acetoxy-phenyl)-1-amino-6-chloro-7-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-phenyl ester
98 N-{4-[3-(4-Acetylamino-phenyl)-1-amino-6-chloro-7-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-phenyl}-acetamide
99 N-{4-[1-Amino-6-chloro-3-(4-methanesulfonylamino-phenyl)-7-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-phenyl}-methanesulfonamide
100 Acetic acid 4-[3-(4-acetoxy-phenyl)-1-acetylamino-6-chloro-7-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-phenyl ester
101 N-[3,3-Bis-(4-amino-phenyl)-6-chloro-7-methyl-2-oxo-2,3-dihydro-indol-1-yl]-acetamide
102 N-[6-Chloro-3,3-bis-(4-dimethylamino-phenyl)-7-methyl-2-oxo-2,3-dihydro-indol-1-yl]-acetamide
103 N-[3,3-Bis-(4-acetylamino-phenyl)-6-chloro-7-methyl-2-oxo-2,3-dihydro-indol-1-yl]-acetamide
104 N-[6-Chloro-3,3-bis-(4-methanesulfonylamino-phenyl)-7-methyl-2-oxo-2,3-dihydro-indol-1-yl]-acetamide
105 6-Chloro-3,3-bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-indole-2-thione
106 Acetic acid 4-[3-(4-acetoxy-phenyl)-6-chloro-7-methyl-2-thioxo-2,3-dihydro-1H-indol-3-yl]-phenyl ester
107 3,3-Bis-(4-amino-phenyl)-6-chloro-7-methyl-1,3-dihydro-indole-2-thione
108 6-Chloro-3,3-bis-(4-dimethylamino-phenyl)-7-methyl-1,3-dihydro-indole-2-thione
109 N-{4-[3-(4-Acetylamino-phenyl)-6-chloro-7-methyl-2-thioxo-2,3-dihydro-1H-indol-3-yl]-phenyl}-acetamide
110 Methanesulfonic acid 4-[6-chloro-3-(4-methanesulfonyloxy-phenyl)-7-methyl-2-thioxo-2,3-dihydro-1H-indol-3-yl]-phenyl ester
111 Acetic acid 4-[4-(4-acetoxy-phenyl)-2-chloro-5-thioxo-5,6-dihydro-4H-thieno[2,3-b]pyrrol-4-yl]-phenyl ester
112 Acetic acid 4-[4-(4-acetoxy-phenyl)-2-chloro-5-thioxo-5,6-dihydro-4H-furo[2,3-b]pyrrol-4-yl]-phenyl ester
113 6,6-Bis-(4-amino-phenyl)-2-chloro-3-methyl-4,6-dihydro-thieno[3,2-b]pyrrole-5-thione
114 2-Chloro-6,6-bis-(4-dimethylamino-phenyl)-3-methyl-4,6-dihydro-3H-pyrrolo[2,3-d]imidazole-5-thione
115 N-{4-[6-(4-Acetylamino-phenyl)-3-chloro-5-thioxo-1,4,5,6-tetrahydro-pyrrolo[3,2-c]pyrazol-6-yl]-phenyl}-acetamide
116 Methanesulfonic acid 4-[2-chloro-4-(4-methanesulfonyloxy-phenyl)-5-thioxo-5,6-dihydro-4H-furo[2,3-b]pyrrol-4-yl]-phenyl ester
117 6-Chloro-7-cyclopropyl-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one
118 6-Chloro-7-cyclopropyl-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one
119 6-Chloro-3,3-bis-(4-hydroxy-phenyl)-7-trifluoromethyl-1,3-dihydro-indol-2-one
120 6-Chloro-3,3-bis-(4-hydroxy-phenyl)-7-trifluoromethyl-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one
121 6-Chloro-7-cyclopropoxy-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one
122 6-Chloro-7-cyclopropoxy-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one
123 6-(4-Fluoro-phenoxy)-3,3-bis-(4-hydroxy-phenyl)-7-trifluoromethyl-1,3-dihydro-indol-2-one
124 Acetic acid 4-[3-(4-acetoxy-phenyl)-6-chloro-7-cyclopropyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-phenyl ester
125 Acetic acid 4-[3-(4-acetoxy-phenyl)-6-chloro-7-cyclopropyl-2-oxo-2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-3-yl]-phenyl ester
126 Acetic acid 4-[3-(4-acetoxy-phenyl)-6-chloro-2-oxo-7-trifluoromethyl-2,3-dihydro-1H-indol-3-yl]-phenyl ester
127 Acetic acid 4-[3-(4-acetoxy-phenyl)-6-chloro-2-oxo-7-trifluoromethyl-2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-3-yl]-phenyl ester
128 Acetic acid 4-[3-(4-acetoxy-phenyl)-6-chloro-7-cyclopropoxy-2-oxo-2,3-dihydro-1H-indol-3-yl]-phenyl ester
129 Acetic acid 4-[3-(4-acetoxy-phenyl)-6-chloro-7-cyclopropoxy-2-oxo-2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-3-yl]-phenyl ester

130 Acetic acid 4-[3-(4-acetoxy-phenyl)-6-(4-fluoro-phenoxy)-2-oxo-7-trifluoromethyl-2,3-dihydro-1H-indol-3-yl]-phenyl ester
131 Dimethylamino-acetic acid 4-{6-chloro-7-cyclopropyl-3-[4-(2-dimethylamino-acetoxy)-phenyl]-2-oxo-2,3-dihydro-1H-indol-3-yl}-phenyl ester
132 Dimethylamino-acetic acid 4-{6-chloro-7-cyclopropyl-3-[4-(2-dimethylamino-acetoxy)-phenyl]-2-oxo-2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-3-yl}-phenyl ester
133 Dimethylamino-acetic acid 4-{6-chloro-3-[4-(2-dimethylamino-acetoxy)-phenyl]-7-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl}-phenyl ester
134 6-Chloro-3,3-bis-(4-hydroxy-phenyl)-7-trifluoromethoxy-1,3-dihydro-indol-2-one
135 Acetic acid 4-[3-(4-acetoxy-phenyl)-6-chloro-2-oxo-7-trifluoromethoxy-2,3-dihydro-1H-indol-3-yl]-phenyl ester
136 Dimethylamino-acetic acid 4-{6-chloro-3-[4-(2-dimethylamino-acetoxy)-phenyl]-2-oxo-7-trifluoromethoxy-2,3-dihydro-1H-indol-3-yl}-phenyl ester
137 6-Chloro-4-fluoro-3,3-bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-indol-2-one
138 3-Chloro-7,7-bis-(4-hydroxy-phenyl)-4-methyl-5,7-dihydro-pyrrolo[3,2-c]pyridazin-6-one
139 Acetic acid 4-[3-(4-acetoxy-phenyl)-6-chloro-4-fluoro-7-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-phenyl ester
140 Acetic acid 4-[3-(4-acetoxy-phenyl)-6-chloro-4,7-dimethyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-phenyl ester
141 Acetic acid 4-[7-(4-acetoxy-phenyl)-3-chloro-4-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[3,2-c]pyridazin-7-yl]-phenyl ester
142 6-Chloro-4,5-difluoro-3,3-bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-indol-2-one
143 Acetic acid 4-[3-(4-acetoxy-phenyl)-6-chloro-4,5-difluoro-7-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-phenyl ester
144 3,3-Bis-(4-hydroxy-phenyl)-3,6,7,8-tetrahydro-1H-1-aza-as-indacen-2-one
145 3,3-Bis-(4-hydroxy-phenyl)-1,3,6,7,8,9-hexahydro-benzo[g]indol-2-one
146 3,3-Bis-(4-hydroxy-phenyl)-7-trifluoromethyl-1,3-dihydro-indol-2-one
147 7-Chloro-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one
148 3,3-Bis-(4-hydroxy-phenyl)-2-oxo-2,3-dihydro-1H-indole-7-carbonitrile
149 7-Ethyl-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one
150 3,3-Bis-(4-hydroxy-phenyl)-7-morpholin-4-yl-1,3-dihydro-indol-2-one
151 3,3-Bis-(4-hydroxy-phenyl)-7-isopropyl-1,3-dihydro-indol-2-one
152 7-tert-Butyl-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one
153 3,3-Bis-(4-hydroxy-phenyl)-2-oxo-2,3-dihydro-1H-indole-7-carboxylic acid dimethylamide
154 3,3-Bis-(4-hydroxy-phenyl)-7-(4-methyl-piperazine-1-carbonyl)-1,3-dihydro-indol-2-one
155 3,3-Bis-(4-hydroxy-phenyl)-2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid
156 3,3-Bis-(4-hydroxy-phenyl)-2-oxo-2,3-dihydro-1H-indole-5-carboxylic acid dimethylamide
157 3,3-Bis-(4-hydroxy-phenyl)-5-(morpholine-4-carbonyl)-1,3-dihydro-indol-2-one
158 3,3-Bis-(4-hydroxy-phenyl)-4-methoxy-1,3-dihydro-indol-2-one
159 3,3-Bis-(4-hydroxy-phenyl)-6-methoxy-1,3-dihydro-indol-2-one
160 3,3-Bis-(4-hydroxy-phenyl)-5-(4-methyl-piperazine-1-carbonyl)-1,3-dihydro-indol-2-one
161 6-Chloro-3,3-bis-(4-mercapto-phenyl)-7-methyl-1,3-dihydro-indol-2-one
162 N-{4-[3-(4-Acetylamino-phenyl)-7-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-phenyl}-acetamide
163 3,3-Bis-(4-hydroxy-phenyl)-7-(3-methoxy-prop-1-ynyl)-1,3-dihydro-indol-2-one
164 3,3-Bis-(4-hydroxy-phenyl)-7-pyridin-3-yl-1,3-dihydro-indol-2-one
165 7-Bromo-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one
166 6-Chloro-3,3-bis-(4-methanesulfonyl-phenyl)-7-methyl-1,3-dihydro-indol-2-one
167 6,6-Bis-(4-hydroxy-phenyl)-4,6-dihydro-pyrrolo[3,2-d]thiazol-5-one
168 6,6-Bis-(4-hydroxy-phenyl)-2-methyl-4,6-dihydro-pyrrolo[3,2-d]thiazol-5-one
169 6,6-Bis-(4-hydroxy-phenyl)-2-isopropyl-4,6-dihydro-pyrrolo[3,2-d]thiazol-5-one
170 2-Chloro-6,6-bis-(4-hydroxy-phenyl)-4,6-dihydro-pyrrolo[3,2-d]thiazol-5-one
171 4,4-Bis-(4-hydroxy-phenyl)-4,6-dihydro-pyrrolo[3,2-d]isothiazol-5-one
172 3,3-Bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-pyrrolo[2,3-c]pyridin-2-one
173 3,3-Bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-pyrrolo[3,2-b]pyridin-2-one
174 3,3-Bis-(4-fluoro-phenyl)-7-methyl-1,3-dihydro-pyrrolo[3,2-b]pyridin-2-one
175 3,3-Bis-(4-fluoro-phenyl)-7-methyl-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one
176 3,3-Bis-(4-fluoro-phenyl)-7-isopropyl-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one
177 3,3-Bis-(4-hydroxy-phenyl)-3,6,7,8-tetrahydro-1H-1,5-diaza-as-indacen-2-one
178 3,3-Bis-(4-hydroxy-phenyl)-3,6,7,8-tetrahydro-1H-1,4-diaza-as-indacen-2-one
179 3,3-Bis-(4-hydroxy-phenyl)-1,3,6,7,8,9-hexahydro-pyrrolo[3,2-c]quinolin-2-one
180 3,3-Bis-(4-hydroxy-phenyl)-1,3,6,7,8,9-hexahydro-pyrrolo[3,2-c]isoquinolin-2-one
181 5-Fluoro-3,3-bis-(4-hydroxy-phenyl)-3,6,7,8-tetrahydro-1H-1-aza-as-indacen-2-one
182 7-Ethyl-5-fluoro-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one

183 3,3-Bis-(4-hydroxy-phenyl)-1,3,6,8-tetrahydro-7-oxa-1-aza-as-indacen-2-one
184 3,3-Bis-(4-hydroxy-phenyl)-1,3,7,8-tetrahydro-6-oxa-1-aza-as-indacen-2-one
185 3,3-Bis-(4-hydroxy-phenyl)-1,6,7,9-tetrahydro-3H-8-oxa-1-aza-cyclopenta[a]naphthalen-2-one
186 3,3-Bis-(4-hydroxy-phenyl)-1,7,8,9-tetrahydro-3H-pyrano[2,3-g]indol-2-one
187 3,3-Bis-(4-hydroxy-phenyl)-7-methyl-3,6,7,8-tetrahydro-1H-1,7-diaza-as-indacen-2-one
188 3,3-Bis-(4-hydroxy-phenyl)-7-methyl-1,3,7,8-tetrahydro-1,7-diaza-as-indacene-2,6-dione
189 3,3-Bis-(4-hydroxy-phenyl)-7,8,8-trimethyl-1,3,7,8-tetrahydro-1,7-diaza-as-indacene-2,6-dione
190 3,3-Bis-(4-hydroxy-phenyl)-5-iodo-1,3-dihydro-indol-2-one
191 5-Amino-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one
192 5-Amino-3,3-bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-indol-2-one
193 6-Bromo-3,3-bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-indol-2-one
194 7-Fluoro-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one
195 3,3-Bis-(4-hydroxy-phenyl)-7-methoxy-1,3-dihydro-indol-2-one
196 4,7-Dichloro-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one
197 6-Chloro-3,3-bis-(4-hydroxy-phenyl)-1,7-dimethyl-1,3-dihydro-indol-2-one
198 6-Chloro-3,3-bis-(4-fluoro-phenyl)-7-methyl-1,3-dihydro-indol-2-one
199 3,3-Bis-(4-hydroxy-phenyl)-7-(morpholine-4-carbonyl)-1,3-dihydro-indol-2-one
200 3,3-Bis-(4-hydroxy-phenyl)-1,3-dihydro-pyrrolo[2,3-d]pyridin-2-one
201 N-{4-[6-Chloro-3-(4-methanesulfonylamino-phenyl)-7-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-phenyl}-methanesulfonamide
202 3,3-Bis-(4-hydroxy-phenyl)-4,7-dimethyl-1,3-dihydro-indol-2-one
203 3,3-Bis-(4-hydroxy-phenyl)-7-iodo-1,3-dihydro-indol-2-one
204 3,3-Bis-(4-hydroxy-phenyl)-7-pyridin-4-yl-1,3-dihydro-indol-2-one
205 Acetic acid 4-[3-(4-acetoxy-phenyl)-6-chloro-7-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-phenyl ester
206 3,3-Bis-(4-hydroxy-phenyl)-5-phenyl-1,3-dihydro-indol-2-one
207 3,3-Bis-(4-hydroxy-phenyl)-7-thiophen-2-yl-1,3-dihydro-indol-2-one
208 3,3-Bis-(4-hydroxy-phenyl)-5-pyridin-4-yl-1,3-dihydro-indol-2-one
209 3,3-Bis-(4-hydroxy-phenyl)-5-thiophen-2-yl-1,3-dihydro-indol-2-one
210 5,7-Difluoro-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one
211 6-Fluoro-3,3-bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-indol-2-one
212 3,3-Bis-(4-hydroxy-phenyl)-6-methoxy-7-methyl-1,3-dihydro-indol-2-one
213 6,7-Difluoro-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one
214 6-Chloro-7-fluoro-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one
215 5-Fluoro-3,3-bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-indol-2-one
216 3,3-Bis-(4-hydroxy-phenyl)-5-methoxy-7-methyl-1,3-dihydro-indol-2-one
217 3,3-Bis-(4-hydroxy-phenyl)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one
218 7-Chloro-3,3-bis-(4-hydroxy-phenyl)-4-methoxy-1,3-dihydro-indol-2-one
219 6-Fluoro-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one
220 N-[3,3-Bis-(4-hydroxy-phenyl)-2-oxo-2,3-dihydro-indol-1-yl]-acetamide
221 5-[3,3-Bis-(4-hydroxy-phenyl)-7-methyl-2-oxo-2,3-dihydro-1H-indol-6-yloxy]-pentanoic acid methyl ester
222 5-[3,3-Bis-(4-hydroxy-phenyl)-7-methyl-2-oxo-2,3-dihydro-1H-indol-6-yloxy]-pentanoic acid
223 5-[3,3-Bis-(4-hydroxy-phenyl)-7-methyl-2-oxo-2,3-dihydro-1H-indol-5-yloxy]-pentanoic acid methyl ester
224 5-[3,3-Bis-(4-hydroxy-phenyl)-7-methyl-2-oxo-2,3-dihydro-1H-indol-5-yloxy]-pentanoic acid
225 7-Chloro-6-fluoro-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one.

Method of treatment

A further aspect of the present invention relates to a method of treating a mammal suffering from or being susceptible to cancer, the method ~~comprising~~including administering to the mammal a therapeutically effective amount of a compound defined hereinabove. Conditions with respect to dosage, administration, etc. may be as defined further below.

Biological effects

The present inventors have found that many compounds of general formula (I) are shown to inhibit the proliferation of MDA-468 cells at lower concentrations ~~asthan~~ those required to inhibit proliferation of MDA-231 cells. A possible mechanism to explain this finding is the selective inhibition of protein synthesis by compounds of general formula (I) in MDA-468 cells compared to MDA-231 cells. Our present hypothesis is that compounds of the general formula (I) inhibit protein synthesis by selective inhibition of mTOR pathway activation and/or other biochemical pathways involved in the regulation of protein synthesis.

The selective inhibition of mTOR pathway activation by compounds of the general formula (I) in Western blots correlates with cell proliferation and protein synthesis data. This suggests that detection of mTOR pathway activity by measurement of either p70S6K, 4E-BP1 or S6K phosphorylation status using phosphor-specific or total protein antibodies by Western blot or ELISA, or measurement of p70S6K kinase activity, in patient tumour material or blood samples, may provide a useful method for selecting patients who will respond to compounds of general formula (I). Alternatively, measurement of p70S6K or S6K phosphorylation status using phosphospecific antibodies, or p70S6K kinase activity, in tumour material or blood samples may provide a biomarker useful for determining drug dosing of compounds of the general formula (I) in human clinical trials.

Compounds for medical use

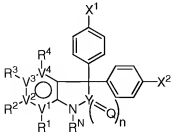
Apart from the more specific medical use outlined above, it is also believed that the majority of the compounds defined herein are generally applicable for medical use.

Thus, in a further aspect the present invention relates to a compound as defined hereinabove for use as a medicament, with the proviso that the compound is not one selected from 3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one and acetic acid 4-[3-(4-acetoxy-phenyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-phenyl ester. Particularly interesting compounds of the Formula ~~(I)~~(I) are those of the formulae (IIa), (IIb), (IIc) and (IId) defined above.

Novel compounds

As mentioned in the introductory section, a few compounds according to the general formula (I) have been described in the literature and (unrelated) biological effects have previously been described for some of these compounds.

Thus, a still further aspect of the present invention relates to a compound of the formula (I)



(I)

as defined further above, with the proviso that the compound is not one selected from
3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one,
3,3-bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-indol-2-one;
3,3-bis-(4-hydroxy-phenyl)-4,5-dimethyl-1,3-dihydro-indol-2-one ;
3,3-bis-(4-hydroxy-phenyl)-5,7-dimethyl-1,3-dihydro-indol-2-one;
5-bromo-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one;
5-chloro-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one;
3,3-bis-(4-hydroxy-phenyl)-5-methoxy-1,3-dihydro-indol-2-one;
3,3-bis-(4-hydroxy-phenyl)-5-methyl-1,3-dihydro-indol-2-one;
6-chloro-3,3-bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-indol-2-one;
acetic acid 4-[3-(4-acetoxy-phenyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-phenyl ester; and
acetic acid 4-[3-(4-acetoxy-phenyl)-5-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-phenyl ester.

The specification of the compound of the formula (I) and the preferences are as described hereinabove. In particular, preferred compounds of the Formula ~~(I)~~ (I) are those of the formulae (IIa), (IIb), (IIc) and (IId) defined above.

Preparation of compounds of the formula (I) and the formula (IIa)-(IId)

The compounds generally can be synthesized as described in the Examples section.

Formulation of pharmaceutical compositions

The compound of the formula (I) (and the more specific compound of the formula (II)) is suitably formulated in a pharmaceutical composition so as to suit the desirable route of administration.

The administration route of the compounds may be any suitable route which leads to a concentration in the blood or tissue corresponding to a ~~therapeutic~~therapeutically effective concentration. Thus, e.g., the following administration routes may be applicable although the invention is not limited thereto: the oral route, the parenteral route, the cutaneous route, the nasal route, the rectal route, the vaginal route and the ocular route. It should be clear to a person skilled in the art that the administration route is dependent on the particular compound in question; particularly the choice of administration route depends on the physico-chemical properties of the compound together with the age and weight of the patient and on the particular disease or condition and the severity of the same.

The compounds may be contained in any appropriate amount in a pharmaceutical composition, and are generally contained in an amount of about 1-95%, e.g. 1-10%, by weight of the total weight of the composition. The composition may be presented in a dosage form which is suitable for the oral, parenteral, rectal, cutaneous, nasal, vaginal and/or ocular administration route. Thus, the composition may be in form of, e.g., tablets, capsules, pills, powders, granulates, suspensions, emulsions, solutions, gels including hydrogels, pastes, ointments, creams, plasters, drenches, delivery devices, suppositories, enemas, injectables, implants, sprays, aerosols and in other suitable form.

The pharmaceutical compositions may be formulated according to conventional pharmaceutical practice, see, e.g., "Remington's Pharmaceutical Sciences" and "Encyclopedia of Pharmaceutical Technology", edited by Swarbrick, J. & J. C. Boylan, Marcel Dekker, Inc., New York, 1988. Typically, the compounds defined herein are formulated with (at least) a pharmaceutically acceptable carrier or excipient. Pharmaceutically acceptable carriers or excipients are those known by the person skilled in the art. Formation of suitable salts of the compounds of the Formula I(I) will also be evident in view of the before-mentioned.

Thus, the present invention provides in a further aspect a pharmaceutical composition ~~comprising~~containing a compound of the general Formula I(I) in combination with a pharmaceutically acceptable carrier.

The compound is preferably one of those defined under "Compounds for medical use".

In a particular embodiment, the compound is as defined under "Novel compounds", i.e. novel compounds of the Formula (I) and Formula (II) respectively.

Pharmaceutical compositions according to the present invention may be formulated to release the active compound substantially immediately upon administration or at any substantially

predetermined time or time period after administration. The latter type of compositions is generally known as controlled release formulations.

In the present context, the term "controlled release formulation" embraces i) formulations which create a substantially constant concentration of the drug within the body over an extended period of time, ii) formulations which after a predetermined lag time create a substantially constant concentration of the drug within the body over an extended period of time, iii) formulations which sustain drug action during a predetermined time period by maintaining a relatively, constant, effective drug level in the body with concomitant minimization of undesirable side effects associated with fluctuations in the plasma level of the active drug substance (sawtooth kinetic pattern), iv) formulations which attempt to localize drug action by, e.g., spatial placement of a controlled release composition adjacent to or in the diseased tissue or organ, and v) formulations which attempt to target drug action by using carriers or chemical derivatives to deliver the drug to a particular target cell type.

Controlled release formulations may also be denoted "sustained release", "prolonged release", "programmed release", "time release", "rate-controlled" and/or "targeted release" formulations.

Controlled release pharmaceutical compositions may be presented in any suitable dosage forms, especially in dosage forms intended for oral, parenteral, cutaneous, nasal, rectal, vaginal and/or ocular administration. Examples include single or multiple unit tablet or capsule compositions, oil solutions, suspensions, emulsions, microcapsules, microspheres, nanoparticles, liposomes, delivery devices such as those intended for oral, parenteral, cutaneous, nasal, vaginal or ocular use.

Preparation of solid dosage forms for oral use, controlled release oral dosage forms, fluid liquid compositions, parenteral compositions, controlled release parenteral compositions, rectal compositions, nasal compositions, percutaneous and topical compositions, controlled release percutaneous and topical compositions, and compositions for administration to the eye will be well-known to those skilled in the art of pharmaceutical formulation. Specific formulations can be found in "Remington's Pharmaceutical Sciences".

Capsules, tablets and pills etc. may contain for example the following compounds: microcrystalline cellulose, gum or gelatin as binders; starch or lactose as excipients; stearates as lubricants; various sweetening or flavouring agents. For capsules the dosage unit may contain a liquid carrier like fatty oils. Likewise coatings of sugar or enteric agents may be part of the dosage unit. The pharmaceutical compositions may also be emulsions of the compound(s) and a lipid forming a micellular emulsion.

For parenteral, subcutaneous, intradermal or topical administration the pharmaceutical composition may include a sterile diluent, buffers, regulators of tonicity and antibacterials. The active compound may be prepared with carriers that protect against degradation or immediate elimination from the body, including implants or microcapsules with controlled release properties. For intravenous administration the preferred carriers are physiological saline or phosphate buffered saline.

Dosages

In one embodiment, the pharmaceutical composition is in unit dosage form. In such embodiments, each unit dosage form typically comprises 0.1-500 mg, such as 0.1-200 mg, e.g. 0.1-100 mg, of the compound.

More generally, the compound ~~are~~is preferably administered in an amount of about 0.1-250 mg per kg body weight per day, such as about 0.5-100 mg per kg body weight per day.

For compositions adapted for oral administration for systemic use, the dosage is normally 0.5 mg to 1 g per dose administered 1-4 times daily for 1 week to 12 months depending on the disease to be treated.

The dosage for oral administration of the composition in order to prevent diseases or conditions is normally 1 mg to 100 mg per kg body weight per day. The dosage may be administered once or twice daily for a period starting 1 week before the exposure to the disease until 4 weeks after the exposure.

For compositions adapted for rectal use for preventing diseases, a somewhat higher amount of the compound is usually preferred, i.e. from approximately 1 mg to 100 mg per kg body weight per day.

For parenteral administration, a dose of about 0.1 mg to about 100 mg per kg body weight per day is convenient. For intravenous administration, a dose of about 0.1 mg to about 20 mg per kg body weight per day administered for 1 day to 3 months is convenient. For intraarticular administration, a dose of about 0.1 mg to about 50 mg per kg body weight per day is usually preferable. For parenteral administration in general, a solution in an aqueous medium of 0.5-2% or more of the active ingredients may be employed.

For topical administration on the skin, a dose of about 1 mg to about 5 g administered 1-10 times daily for 1 week to 12 months is usually preferable.

Combination treatment

In an intriguing embodiment of the present invention, the compound of the general formula (I) or the general formula (II) is used therapeutically in combination with one or more other chemotherapeutic agents. Examples of such chemotherapeutic agents are those selected from daunorubicin, docetaxel, prednisone, dexamethasone, decadron, altretamine, amifostine, aminoglutethimide, dactinomycin, anastrozole, asparaginase, bicalutamide, bleomycin, busulfan, carboplatin, carmustine, chlorambucil, chlorodeoxyadenosine, cisplatin, cytosine arabinoside, dacarbazine, doxorubicin, epirubicin, estramustine, diethylstilbestrol, fludarabine, flutamide, 5-fluorouracil, gemcitabine, goserelin, idarubicin, irinotecan, levamisole, lomustine, mechlorathamine, alkeran, mercaptopurine, taxol (e.g. paclitaxel). In particular, the further chemotherapeutic agent is selected from taxanes such as Taxol, Paclitaxel and Docetaxel.

Thus, with respect to the use and the method of treatment defined herein, the medicament may further ~~comprise~~contain one or more other chemotherapeutic agents.

With respect to the pharmaceutical composition defined herein, such a composition may further ~~comprise~~contain one or more other chemotherapeutic agents.

EXAMPLES

Materials:

The following cell lines were obtained from ATCC: MDA-MB-231, MDA-MB-435S, MDA-MB-453, MDA-MB-468, SKBr-3, BT-474, BT-549, MCF-7, MCF10A, T-47D, ZR75-1, HCC-1954, DU-145, PC-3, LnCaP, and Colo205. PC-3/M was obtained from NCI. Terfenadine was obtained from Sigma-Aldrich. Penicillin-Streptomycin and gentamicin was purchased from Invitrogen. Alamar Blue reagent is from BioSource.

Starting materials, reagents and solvents for the chemical syntheses were obtained from commercial sources unless otherwise stated. Oxyphenisatine (Commercial A) and 7-methyl-oxyphenisatine (Commercial B) were also obtained from ~~commercials~~commercial sources.

Example 1: Procedures for preparation of isatin derivatives

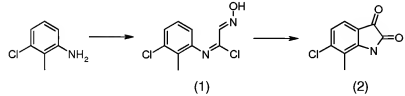
Isatin derivatives used as intermediates can be obtained by either Protocol A or Protocol B.

Protocol A, based on literature procedures, was used to generate aromatic isatins with either electron-donating substituents (see Stolle: *J. Prakt. Chem.* (1922), **105**, 137 and Sandmeyer: *Helv. Chim. Acta* (1919), **2**, 234) or a 5-membered electron rich heteroaromatic moiety (see Shvedov et al.: (Chem.Chem. Heterocycl. Compd. Engl. Transl. (1975), **11**, 666). Examples of preferred 5-membered heterocycles are thiophenes (V^1=S, V^2=V^3=C(-) and V^4=bond; V^2=S, V^1=V^3=C(-) and V^4=bond or V^3=S, V^1=V^2=C(-) and V^4=bond), furans (V^1=O, V^2=V^3=C(-) and V^4=bond; V^2=O, V^1=V^3=C(-) and V^4=bond or V^3=O, V^1=V^2=C(-) and V^4=bond), pyrazoles (V^1=N(-), V^2=N, V^3=C(-) and V^4=bond; V^1=N, V^2=N(-), V^3=C(-) and V^4=bond) and imidazoles (V^1=N(-), V^2=C(-), V^3=N and V^4=bond; V^1=N, V^2=C(-), V^3=N(-) and V^4=bond).

Protocol B, based on literature procedures, was used to generate aromatic isatins with electron-withdrawing substituents (see Hewawasam and Maenwell: *Tet. Lett.* (1994), **35**, 7303) and 6-membered electron-poor heteroaromatic isatins (see Rivalle and Bisagni: *J. Heterocycl. Chem.* (1997), **34**, 441). Examples of preferred 6-membered heterocycles are pyridines (V^1=N, V^2=V^3=V^4=C(-); V^2=N, V^1=V^3=V^4=C(-); V^3=N, V^1=V^2=V^4=C(-) and V^4=N, V^1=V^2=V^3=C(-)), pyrimidines (V^1=V^3=N, V^2=V^4=C(-); V^2=V^4=N, V^1=V^3=C(-)), pyrazines (V^1=V^4=N, V^2=V^3=C(-)) and pyridazines (V^1=V^2=N, V^3=V^4=C(-); V^2=V^3=N, V^1=V^6=C(-); V^3=V^4=N, V^1=V^2=C(-)).

Other isatins of interest could in addition be prepared using one of the alternative methods published in the literature (see *i.e.* Tatsugi *et al. ARKIVOC* (2001), 67-73 or the review by Silva *et al.* in *J. Braz. Chem. Soc.* (2001), **12**, 273-324).

Protocol A: Preparation of isatin derivatives



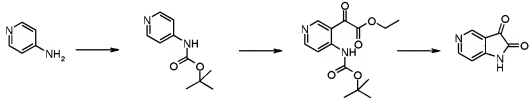
(1) (2)

To a well stirred suspension of sodium sulfate (314.g, 2211 mmol) in water (700 mL) at 60°C were added in sequence hydroxylamine hydrochloride (56 g, 806 mmol), chloral hydrate (47 g, 284 mmol), 2-methyl-3-chloro-aniline (40 g, 283 mmol) in water (500 mL) and finally concentrated hydrochloric acid (12 M, 24.2 ml, 290 mmol). The mixture temperature was risen/raised to 100°C. After 20 minutes, the brown solution was left to cool to room temperature and kept stirring overnight. The solid present was filtered, washed with water

(3X), heptane (2X) and dried at 60°C under vacuum for 6 hours. Obtained 62 g of N-(3-chloro-2-methyl-phenyl)-2-hydroxyimino-acetimidoyl chloride (1) as a beige solid used without further purification. δ_H (400 MHz, DMSO-d6) 12.3 (1 H, s), 9.8 (1 H, s), 7.7 (1 H, s), 7.42 (1 H, d, *J*= 7.8), 7.36 (1 H, d, *J*= 7.6), 7.3 (1 H, m), 2.25 (3 H, s).

To well stirred sulphuric acid (18.3 M, 300 ml) heated at 50°C was added N-(3-chloro-2-methyl-phenyl)-2-hydroxyimino-acetimidoyl chloride (1) in small portion over 20 minutes (exothermic up to 70°C) (60 g, 282 mmol). After addition was completed, the temperature was ~~risen~~raised to 80°C and kept for 20 minutes after which the reaction was left cool to room temperature. The brown mixture was slowly poured into ice (~500 g) and water (500 mL), diluted with more water (1 L) to yield a brown-orange slurry. The solid was collected by filtration, washed with water (2X) under suction to yield an orange solid. This solid was dissolved in 0.4 M sodium hydroxide (1 L). All insoluble tar was removed by filtration. Concentrated hydrochloric acid (12 M, 70 mL) was added, the resulting brown-orange solid was collected by filtration, washed with water (3X), heptane (2X) and dried at 54°C under vacuum for 6 hours. Obtained 34.5 g (208 mmol, 62%) of 6-chloro-7-methyl-1H-indole-2,3-dione (2). δ_H (400 MHz, DMSO-d6) 11.3 (1 H, s), 7.4 (1 H, d, *J*=8.0), 7.2 (1 H, d, *J*=8.1), 2.25 (3 H, s).

Protocol B: Preparation of isatin derivatives



To a well stirred solution of Boc anhydride (2.56 g, 11.7 mmol) in THF (10 mL) was added 4-aminopyridine (1.0 g, 10.6 mmol) in portions over 3 minutes while maintaining the temperature between 20ºC and 25ºC. No more exotherm was observed after 5 minutes. The reaction was then stirred at room temperature for 3.5 hours. After *in vacuo* concentration the crude mixture was then ~~titurated~~triturated in hexane (20 mL), filtered and washed with more hexane (~5 mL). The resulting solid was dried under reduced pressure to yield 1.93 g (9.9 mmol, 94%) of pyridin-4-yl-carbamic acid tert-butyl ester as a white solid and was used without further purification. LCMS (BDS-Hypersil C_{18}, 50 mm X 2.1 mm, 5 µ, 2.5 minutes) m/z 195 $[MH]^+$ @ retension time 0.90 minutes, 100% by UV at 215 nm.

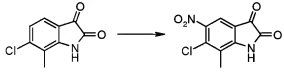
To a stirred solution of pyridin-4-yl-carbamic acid *tert*-butyl ester (0.62 g, 3.09 mmol) in THF (9 mL) cooled to -5ºC was slowly added a solution of t-BuLi (1.7M in THF, 5.5 mL, 9.27 mmol) over 17 minutes while maintaining the temperature between -5ºC and 1ºC. A red brown precipitate resulted and the reaction mixture was stirred at 0ºC for a further 1.5 hours. The reaction mixture was then cooled back down to -5ºC and diethyloxalate (1.3 mL, 9.27 mmol) was added. The reaction was allowed to reach room temperature and then after 2 hours quenched with water (10 mL). After *in vacuo* concentration the resulting mixture was diluted in ethyl acetate (20 mL) and washed with water (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/ Hexane) afforded 0.16 g (0.54 mmol, 17%) of (4-tert-butoxycarbonylamino-pyridin-3-yl)-oxo-acetic acid ethyl ester as a brown oil.

LCMS (BDS-Hypersil C_{18}, 50 mm X 2.1 mm, 5 µ, 2.5 minutes) m/z 295 $[MH]^+$ + H_2O adduct @ retension time 1.07 minute, 96% by UV at 215 nm.

(4-tert-Butoxycarbonylamino-pyridin-3-yl)-oxo-acetic acid ethyl ester (0.14 g, 0.476 mmol) was heated at 186ºC under 5 mmHg for 25 minutes in a Kugelrohr apparatus. The brown oil ~~darkensdarkened~~ and subsequently ~~givesgave~~ off gases to form a dark green solid. The solid was dissolved in MeOH and concentrated *in vacuo* to yield 0.04 g (0.3 mmol, 56%) of 1H-pyrrolo[3,2-c]pyridine-2,3-dione as a dark solid. The isatin was then taken to the next step without further purification.

Protocol C: Introduction of functional groups on the isatin derivatives

6-Chloro-7-methyl-5-nitro-1H-indole-2,3-dione (4)



(2) (4)

To a well stirred suspension of 2 (2.0 g, 10.2 mmol) in glacial acetic acid (2 mL) and sulphuric acid (4 mL) cooled in ice/water was added a cold mixture of nitric acid (69%, 1 g, 10.9 mmol) and sulphuric acid (0.7 g, 7.3 mmol) at such a rate as to maintain internal temperature below 5°C. After addition was completed reaction mixture was stirred at room temperature for 1 h, then slowly poured over ice (~20 g) and left standing for 10 minutes. The solid formed was collected by filtration, washed with cold water (3X), dried under

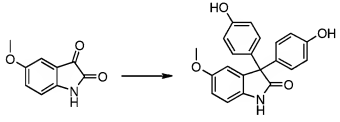
vacuum overnight to yield 1.92 g (8.0 mmol, 78%) of 6-chloro-7-methyl-5-nitro-1H-indole-2,3-dione (4) as an orange solid. LCMS m/z 118.79 [Fragment]$^+$ @ R_T 1.14min, 95%.

Example 2: Procedures for preparation of the final compounds of the invention

The obtained isatin derivatives were used to generate the final compounds of the invention. Typically, an isatin derivative was heated with a benzene derivative to 100 °C in a mixture of glacial acetic acid and sulphuric acid under nitrogen. Alternatively, the isatin derivative was reacted at room temperature with a benzene derivative in triflic acid under nitrogen (see Klumpp *et al. J. Org. Chem*. (1998), **63**, 4481-84). Thioamide derivatives of the final compounds (Q=S and n=1) were obtained by reacting the corresponding amides (Q=O and n=1) with Lawesson's reagent as described in Organic Synthesis Coll. Vol. VII, p372.

Protocol D: Preparation of the final compounds

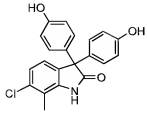
(a)



(7)

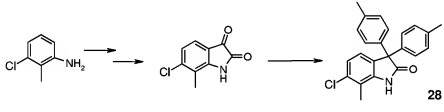
To a suspension of phenol (0.28 g, 2.9 mmol) and 5-methoxy-1H-indole-2,3-dione (0.24 g, ~~(1.3 mmol)~~1.3 mmol) in glacial acetic acid (1.5 ml) under nitrogen was added sulphuric acid (18.3 M, 0.145 mL). The mixture was heated at 100°C for 2 hours. Crude reaction mixture was diluted with water and extracted with ethyl acetate (2X). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to yield a brown solid. This solid was mixed with DCM:AcOEt (9:1) (3X) and gave 0.08 g (0.35 mmol, 18%) of 3,3-bis-(4-hydroxyphenyl)-5-methoxy-1,3-dihydro-indol-2-one (7). LCMS m/z 348.19 [M+H]$^+$ @ R_T 1.09 min, 100%. δ_H (400 MHz, Methanol-d4) 6.92 (4 H, d, *J*=8.80 Hz), 6.79 - 6.82 (1 H, m), 6.69 - 6.73 (1 H, m), 6.61 (5 H, m), 3.62 (3 H, s).

(b)



Phenol (15.3 g, 163.6 mmol) and 6-chloro-7-methyl-1H-indole-2,3-dione (16.0 g, 81.8 mmol) were suspended in glacial acetic acid (82 ml) and sulphuric acid (18.3 M, 8.8 mL) under nitrogen atmosphere. The reaction mixture was heated at 85°C, after 2 hourhours left to cool to room temperature, diluted in ethyl acetate and washed with water (3X). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by re-crystallization from toluene: ethyl acetate (20 volume: 1 volume) to yield 13.3 g of yellow solid containing sole toluene. Dried overnight in high vacuum at 45°C to yield 10.65 g (29.2 mmol, 38 %) of 6-chloro-3,3-bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-indol-2-one (3) as a white solid. LCMS (λ 215 nm, BDS-Hypersil C_{18}, 50 mm X 2.1 mm, 5 µ, 2.5 minute) m/z 366.3 $[(Cl^{35}) M+H]^+$ @ R_T 1.3 min, 100%. δ_H (400 MHz, DMSO-d6) 10.9 (1 H, s), 9.5 (2 H, s), 7.1 (1 H, d, *J*=9.8), 7.05 (1 H, d, *J*=9.6), 6.95 (4 H, d, *J*=10.2), 6.7 (4 H, d, *J*=10.2), 2.35 (3 H, s).

Protocol E: Preparation of the final compounds



28

To a well stirred suspension of 6-chloro-7-methyl-1H-indole-2,3-dione (0.15 g, 0.76 mmol) in toluene (anhydrous) (1 mL) was added trifluromethane sulfonic acid (1.25 mL). The tube was sealed and the mixture was stirred at room temperature for 12 hours. The dark brown reaction mixture was then slowly poured over ice (~10 g) and left standing for 10 minutes. The formed precipitate was collected by filtration, washed with cold water (3X 100 mL), dried under vacuum. Purification by flash column chromatography (gradient elution with EtOAc/Heptane (1:9 to 1:1)) followed by recrystallisation (MeOH/EtOAc) gave 25.2 mg (0.07 mmol, 9%) of 6-chloro-7-methyl-3,3-di-p-tolyl-1,3-dihydro-indol-2-one (28) as a light brown solid.

LCMS (BDS-Hypersil C_{18}, 50 mm X 2.1 mm, 5 μ, 2.5 minutes) m/z major 362.12 $[MH]^+$ and minor 403.17 $[MH+MeCN]^+$ @ retension time 2.18 minutes, 100% by UV at 215 nm.

δ_H (400 MHz, DMSO-d6) 2.24 (6 H, s) 2.28 (3 H, s) 7.00 - 7.03 (5 H, m) 7.05 - 7.12 (5 H, m) 10.96 (1 H, s).

The following compounds were all prepared according to Protocols D or E, unless otherwise specified.

6-Chloro-3,3-bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-indol-2-one (3)
See protocol D.

6-Chloro-3,3-bis-(4-hydroxy-phenyl)-7-methyl-5-nitro-1,3-dihydro-indol-2-one (5)
LCMS m/z 411.1 $[(Cl^{35})\ M+H]^+$ @ R_T 1.26 min, 93%. δ_H (400 MHz, DMSO-d6) 7.48 (1 H, s), 6.96 – 6.96 (4 H, m), 6.66 – 6.59 (4 H, m), 2.35 (3 H, s).

5-Amino-6-chloro-3,3-bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-indol-2-one (6)
To a solution of 5 (0.1 g, 0.24 mmol) in methanol (2 mL) was added Pd/C (10% w/w, 0.03 g). The black mixture was stirred under hydrogen at room temperature for 16 hours. The catalyst was removed by filtration, and the solvent was removed under reduced pressure to yield 0.084 g (0.22 mmol, 92%) of 5-Amino-6-chloro-3,3-bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-indol-2-one (6). LCMS m/z 381.16 $[(Cl^{35})\ M+H]^+$ @ R_T 0.94 min, 84%. δ_H (400 MHz, DMSO-d6) 11.7 (1 H, s), 8.1 (1 H, s), 2.3 (3 H, s).

3,3-Bis-(4-hydroxy-phenyl)-5-methoxy-1,3-dihydro-indol-2-one (7)
See protocol D.

3,3-Bis-(4-hydroxy-phenyl)-5-trifluoromethoxy-1,3-dihydro-indol-2-one (8)
LCMS m/z 402.12 $[M+H]^+$ @ R_T 1.27 min, 96%. δ_H (400 MHz, DMSO-d6) 10.78 (1 H, s), 9.43 (2 H, s), 7.23 (1 H, d, *J*=8.56), 7.17 (1 H, s), 6.99 (1 H, d, *J*=8.56), 6.93 (4 H, d, *J*=8.80), 6.66 (4 H, d, *J*=8.56).

3,3-Bis-(4-hydroxy-phenyl)-5,7-dimethyl-1,3-dihydro-indol-2-one (9)
LCMS m/z 346.19 $[M+H]^+$ @ R_T 1.24 min, 92%. δ_H (400 MHz, DMSO-d6) 10.39 (1 H, s), 9.25 (2 H, s), 6.8 (4 H, d, *J*=8.6), 6.70 (1 H, s), 6.68 (1 H, s), 6.52 (4 H, d, *J*=8.6), 2.09 (6 H, s).

3,3-Bis-(4-hydroxy-phenyl)-2-oxo-2,3-dihydro-1H-indole-7-carboxylic acid (10)
LCMS m/z 362.13 $[M+H]^+$ @ R_T 1.06 min, 90%. δ_H (400 MHz, DMSO-d6) 10.11 (1 H, s), 9.43 (2 H, s), 7.71 (1 H, dd, *J*=8.1, 1.2), 7.38 (1 H, dd, *J*=7.3, 0.7), 7.08 (1 H, t, *J*=7.8), 6.92 (4 H, d, *J*=8.8), 6.67 (4 H, d, *J*=8.8).

5-Chloro-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one (11)
LCMS m/z 352.11 $[(Cl^{35})\ M+H]^+$ @ R_T 1.21 min, 100%. δ_H (400 MHz, DMSO-d6) 10.72 (1 H, s), 9.42 (2 H, s), 7.25 (1 H, dd, *J*=8.2, 2.1), 7.18 (1 H, d, *J*=2.2), 6.89-6.95 (5 H, m), 6.68 (4 H, d, *J*=8.6).

5-Fluoro-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one (12)
LCMS m/z 336.16 $[M+H]^+$ @ R_T 1.14 min, 90%. δ_H (400 MHz, DMSO-d6) 10.61 (1 H, s), 9.41 (2 H, s), 7.00-7.10 (2 H, m), 6.93 (4 H, d, *J*=8.6), 6.89 (1 H, dd, *J*=8.4, 4.5), 6.67 (4 H, d, *J*=8.8).

3,3-Bis-(4-hydroxy-phenyl)-5-nitro-1,3-dihydro-indol-2-one (13)
LCMS m/z 362.86 $[M+H]^+$ @ R_T 1.25 min, 93%. δ_H (400 MHz, DMSO-d6) 11.31 (1 H, s), 9.48 (2 H, s), 8.19 (1 H, dd, *J*=8.7, 2.3), 7.90 (1 H, d, *J*=2.2), 7.12 (1 H, d, *J*=8.8), 6.94 (4 H, d, *J*= 8.8), 6.70 (4 H, d, *J*=8.8).

5-Chloro-3,3-bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-indol-2-one (14)
LCMS m/z 365.92 $[(Cl^{35})\ M+H]^+$ @ R_T 1.36 min, 91%. δ_H (400 MHz, DMSO-d6) 10.77 (1 H, s), 9.41 (2 H, s), 7.10 (1 H, d, *J*=1.5), 6.98 (1 H, d, *J*=1.9), 6.91 (4 H, d, *J*=8.6), 6.67 (4 H, d, *J*=8.6), 2.22 (3 H, s).

3,3-Bis-(4-hydroxy-phenyl)-5-methyl-1,3-dihydro-indol-2-one (15)
LCMS m/z 331.97 $[M+H]^+$ @ R_T 1.37 min, 91%. δ_H (400 MHz, DMSO-d6) 10.42 (1 H, s), 9.33 (2 H, s), 6.90-6.97 (2 H, m), 6.88 (4 H, d, *J*=8.6), 6.75 (1 H, d, *J*=7.8), 6.62 (4 H, d, *J*=8.8), 2.17 (3 H, s).

5-Bromo-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one (16)
LCMS m/z 396.05 $[(Br^{79})\ M+H]^+$ @ R_T 1.14 min, 94%. δ_H (400 MHz, MeOD) 7.28 (1 H, dd, *J* =8.3, 2.0), 7.14 (1 H, d, *J* =2.0), 6.88-6.92 (4 H, m), 6.81 (1 H, d, *J*=8.3), 6.60-6.64 (4 H, m).

3,3-Bis-(4-hydroxy-phenyl)-5-iodo-1,3-dihydro-indol-2-one (17)
LCMS m/z 444.01 $[M+H]^+$ @ R_T 1.70 min, 100%. δ_H (250 MHz, MeOD) 6.72 - 6.85 (5 H, m) 6.99 - 7.08 (5 H, m) 7.15 - 7.21 (1 H, m) 7.28 (1 H, t, *J*=7.23 Hz) 7.41 - 7.52 (2 H, m) 7.60 (1H, dd, *J*=8.23, 1.65 Hz).

5-Amino-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one (18)
LCMS m/z 333.13 $[M+H]^+$ @ R_T 1.29 min, 90%. δ_H (250 MHz, Methanol-D4) 6.71 (4 H, d, *J*=8.60 Hz) 6.98 - 7.05 (4 H, m) 7.12 (1 H, d, *J*=8.23 Hz) 7.20 (1 H, d, *J*=1.83 Hz) 7.26 - 7.33 (1 H, m).

5-Amino-3,3-bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-indol-2-one (19)
LCMS m/z 347.14 $[M+H]^+$ @ R_T 1.28 min, 100%. δ_H (400 MHz, Methanol-D4) 7.02 (4 H, d, *J*=8.8 Hz), 6.68 (4 H, d, *J*=8.8 Hz), 6.42 - 6.52 (2 H, m), 2.21 (3 H, s).

6-Bromo-3,3-bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-indol-2-one (20)
LCMS m/z 410.04 $[M+H]^+$ @ R_T 1.39 min, 94%. δ_H (400 MHz, Methanol-D4) 7.22 (1 H, d, *J*=7.8 Hz), 7.00 (4 H, d, *J*=8.8 Hz), 6.85 (1 H, d, *J*=7.8 Hz), 6.69 (4 H, d, *J*=8.8 Hz), 2.35 (3H, s).

3,3-Bis-(4-hydroxy-phenyl)-7-fluoro-1,3-dihydro-indol-2-one (21)
LCMS m/z 336.11 $[M+H]^+$ @ R_T 1.15 min, 97%. δ_H (400 MHz, Methanol-D4) 6.85 - 6.97 (7 H, m), 6.60 (4 H, d, *J*=8.8 Hz).

3,3-Bis-(4-hydroxy-phenyl)-7-methoxy-1,3-dihydro-indol-2-one (22)
LCMS m/z 348.13 $[M+H]^+$ @ R_T 1.14 min, 94%. δ_H (400 MHz, Methanol-D4) 6.95 - 7.06 (5 H, m), 6.89 (1 H, d, *J*=8.3 Hz), 6.75 (1 H, d, *J*=7.8 Hz), 6.68 (4 H, d, *J*=8.8 Hz), 3.89 (3 H, s).

4,7-Dichloro-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one (23)
LCMS m/z 386.04 $[M+H]^+$ @ R_T 1.35 min, 97%. δ_H (400 MHz, Methanol-D4) 7.29 (1 H, d, *J*=8.8 Hz), 7.06 (4 H, d, *J*=8.8 Hz), 6.97 (1 H, d, *J*=8.8 Hz), 6.71 (4 H, d, *J*=8.8 Hz).

6-Chloro-3,3-bis-(4-hydroxy-phenyl)-1,7-dimethyl-1,3-dihydro-indol-2-one (24)
LCMS m/z 380.11 $[M+H]^+$ @ R_T 1.49 min, 100%. δ_H (400 MHz, Methanol-D4) 7.12 (1 H, d, *J*=7.8 Hz), 6.85 - 7.02 (5 H, m), 6.60 - 6.72 (4 H, m), 3.57 (3 H, s), 2.69 (3 H, s).

6-Chloro-3,3-bis-(4-fluoro-phenyl)-7-methyl-1,3-dihydro-indol-2-one (25)
δ_H (400 MHz, Methanol-D4) 7.15 - 7.30 (4 H, m), 6.97 - 7.13 (6 H, m), 2.34 (3 H, s).

3,3-Bis-(4-hydroxy-phenyl)-7-(morpholine-4-carbonyl)-1,3-dihydro-indol-2-one (26)
To 10 (1 eq) dissolved in dimethylformamide was added $SOCl_2$ (3 eq) at 0°C. The mixture was stirred for 1 hour and evaporated to remove excess $SOCl_2$. Morfoline (3 eq) was added and the reaction mixture was left for 3 hours at room temperature. The solvent was removed in vacuo and the 26 purified by filtration through a pad of silica using dichloromethane-MeOH as eluent. LCMS m/z 431.04 $[M+H]^+$ @ R_T 1.13 min, 90%. δ_H (400 MHz, Methanol-D4) 7.19 - 7.29 (2 H, m), 7.11 (1 H, m), 6.97 - 7.05 (4 H, m), 6.64 - 6.75 (4 H, m), 3.69 (8 H, brs).

3,3-Bis-(4-hydroxy-phenyl)-1,3-dihydro-pyrrolo[3,2-c]pyridin-2-one (27)
LCMS (BDS-Hypersil C_{18}, 50 mm X 2.1 mm, 5 µ, 2.5 minutes) m/z 319.28 $[MH]^+$ @ R_T 0.76 min, 100% by UV at 215 nm. δ_H (400 MHz, CD_3OD) 6.63 (4H, d, *J* 8.6 Hz), 6.93 (4H, d, *J* 8.8 Hz), 6.95 (1H, d, *J* 5.4 Hz), 8.10 (1H, s), 8.24 (1H, d, *J* 5.4Hz).

6-Chloro-7-methyl-3,3-di-p-tolyl-1,3-dihydro-indol-2-one (28)
See protocol E.

3,3-Bis-(4-hydroxy-phenyl)-3,6,7,8-tetrahydro-1H-1-aza-as-indacen-2-one (29)
Phenol (1.0 g, 10.84 mmol) was added to crude 3,3-dibromo-1,3-dihydro-pyrrolo[2,3-b]pyridine-2-one (0.15 g, 0.51 mmol, prepared according to Parrick *et al. Tet. Lett.* (1984), **25**, 3099) and the mixture was heated to 100°C for 10 minutes, allowed to cool to room temperature and the excess phenol removed by flash chromatography. The silica adsorbed product was isolated by washing with methanol and concentrating under reduced pressure. The pH was adjusted to approximately 6 using sodium carbonate solution and the crude product isolated by evaporation under reduced pressure. Purification by preparative HPLC provided the title compound (29) (3 mg, 2%). LCMS m/z 358.35 $[M+H]^+$ @ R_T 1.26 min, 89%. δ_H (400 MHz, DMSO-D6) 10.62 (1 H, s), 9.35 (2 H, s), 6.90 - 6.95 (4 H, m), 6.82 - 6.90 (2 H, m), 6.62 - 6.68 (4 H, m), 2.75 - 2.87 (4 H, m), 1.98 - 2.08 (2 H, m).

7-Bromo-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one (30)
LCMS m/z 398.22 $[M+H]^+$ @ R_T 1.22 min, 100%.

N-{4-[6-Chloro-3-(4-methanesulfonylamino-phenyl)-7-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-phenyl}-methanesulfonamide (31)
LCMS m/z 520.27 $[M+H]^+$ @ R_T 1.30 min, 96%. δ_H (400 MHz, DMSO-D6) 11.00 (1 H, s), 9.78 (2 H, s), 6.85 - 7.37 (10 H, m), 2.97 (6 H, s), 2.28 (3 H, s).

7-Ethyl-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one (32)
LCMS m/z 345.97 $[M+H]^+$ @ R_T 1.30 min, 100%.

3,3-Bis-(4-hydroxy-phenyl)-7-iodo-1,3-dihydro-indol-2-one (33)
LCMS m/z 443.82 $[M+H]^+$ @ R_T 1.37 min, 100%.

3,3-Bis-(4-hydroxy-phenyl)-7-chloro-1,3-dihydro-indol-2-one (34)
LCMS m/z 351.56 $[M+H]^+$ @ R_T 1.33 min, 100%. δ_H (400 MHz, Methanol-D4) 7.23 (1 H, dd, *J*=8.3, 1.0 Hz), 7.05 - 7.11 (1 H, m), 6.96 - 7.04 (5 H, m), 6.70 (4 H, d, *J*=8.8 Hz).

3,3-Bis-(4-hydroxy-phenyl)-7-trifluoromethyl-1,3-dihydro-indol-2-one (35)
LCMS m/z 387.98 $[M+H]^+$ @ R_T 1.35 min, 94%. δ_H (400 MHz, Methanol-D4) 7.49 (1 H, d, *J*=8.3 Hz), 7.38 (1 H, d, *J*=7.3 Hz), 7.17 (1 H, t, *J*=7.6 Hz), 7.00 (4 H, d, *J*=8.8 Hz), 6.71 (4 H, d, *J*=8.8 Hz).

Acetic acid 4-[3-(4-acetoxy-phenyl)-6-chloro-7-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-phenyl ester (36)
LCMS m/z 450.10 $[M+H]^+$ @ R_T 1.63 min, 94%.

3,3-Bis-(4-hydroxy-phenyl)-6-methoxy-1,3-dihydro-indol-2-one (37)
LCMS m/z 348.22 $[M+H]^+$ @ R_T 1.14 min, 98%. δ_H (400 MHz, Methanol-D4) 6.95 - 7.05 (5 H, m), 6.63 - 6.74 (4 H, m), 6.53 - 6.61 (2 H, m), 3.77 (3 H, s).

5,7-Difluoro-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one (38)
LCMS m/z 353.95 $[M+H]^+$ @ R_T 1.25 min, 100%. δ_H (400 MHz, Methanol-D4) 7.00 (4 H, d, *J*=8.8 Hz), 6.93 (1 H, td, *J*=9.8, 2.0 Hz), 6.81 (1 H, dd, *J*=8.1, 2.2 Hz), 6.72 (4 H, d, *J*=8.8 Hz).

6-Fluoro-3,3-bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-indol-2-one (39)
LCMS m/z 349.98 $[M+H]^+$ @ R_T 1.28 min, 100%. δ_H (400 MHz, Methanol-D4) 7.00 (4 H, d, *J*=8.8 Hz), 6.93 (1 H, dd, *J*=8.3, 5.4 Hz), 6.61 - 6.76 (5 H, m), 2.21 (3 H, d, *J*=1.0 Hz).

3,3-Bis-(4-hydroxy-phenyl)-6-methoxy-7-methyl-1,3-dihydro-indol-2-one (40)
LCMS m/z 362.00 $[M+H]^+$ @ R_T 1.35 min, 100%. δ_H (400 MHz, Methanol-D4) 7.00 (4 H, d, *J*=8.8 Hz), 6.89 (1 H, d, *J*=8.3 Hz), 6.67 (4 H, d, *J*=8.8 Hz), 6.59 (1 H, d, *J*=8.3 Hz), 3.80 (3H, s), 2.14 (3 H, s).

6,7-Difluoro-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one (41)
LCMS m/z 353.96 $[M+H]^+$ @ R_T 1.35 min, 96%. δ_H (400 MHz, Methanol-D4) 7.00 (4 H, d, *J*=8.8 Hz), 6.82 - 6.96 (2 H, m), 6.70 (4 H, d, *J*=8.8 Hz).

6-Chloro-7-fluoro-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one (42)
LCMS m/z 369.95 $[M+H]^+$ @ R_T 1.30 min, 100%. δ_H (400 MHz, Methanol-D4) 7.10 (1 H, dd, *J*=8.1, 6.6 Hz), 7.00 (4 H, d, *J*=8.8 Hz), 6.95 (1 H, d, *J*=8.8 Hz), 6.70 (4 H, d, *J*=8.8 Hz).

3,3-Bis-(4-hydroxy-phenyl)-2-oxo-2,3-dihydro-1H-indole-7-carbonitrile (43)
Compound 33 (0.35 g, 0.79 mmol) was treated with zinc cyanide (0.14 g, 1.18 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.09 g, 10%) in anhydrous DMF (5 mL). The reaction mixture was degassed by nitrogen bubbling for 15 minutes. The reaction was then heated to 100°C overnight under nitrogen. After cooling to room temperature the reaction was quenched with saturated aqueous $NaHCO_3$. The resulting cloudy suspension was filtered and the filtrate dissolved in a mixture of toluene and ethylacetate (1:1), washed with aq. $NaHCO_3$ (saturated) (2X), water (2X) and dried over sodium sulphate. After filtration the organic layer was concentrated under reduced pressure to give the crude product. Re-treatment of the crude material was carried out a further two times with the same amounts and conditions as above. The compound was initially purified by flash column chromatography (DCM: MeOH with gradient elution 95:5 to 9:1) followed by preparative HPLC to afford the desired compound (43) as a white solid (0.014 g, 5%). LCMS m/z 343.07 $[M+H]^+$ @ R_T 1.15 min, 97%. δ_H (400 MHz, Methanol-D4) 7.51 (1 H, dd, *J*=7.8, 1.0 Hz), 7.41 (1 H, dd, *J*=7.8, 1.0 Hz), 7.13 (1 H, t, *J*=7.8 Hz), 6.99 (4 H, d, *J*=8.8Hz), 6.71 (4 H, d, *J*=8.8 Hz).

5-Fluoro-3,3-bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-indol-2-one (44)
LCMS m/z 350.29 $[M+H]^+$ @ R_T 1.20 min, 95%. δ_H (400 MHz, Methanol-D4) 7.00 (4 H, d, *J*=8.8 Hz), 6.82 (1 H, dd, *J*=10.5, 2.2 Hz), 6.62 - 6.75 (5 H, m), 2.30 (3 H, s).

3,3-Bis-(4-hydroxy-phenyl)-5-methoxy-7-methyl-1,3-dihydro-indol-2-one (45)
LCMS m/z 362.25 $[M+H]^+$ @ R_T 1.16 min, 91%. δ_H (400 MHz, Methanol-D4) 7.01 (4 H, d, *J*=8.8 Hz), 6.69 (4 H, d, *J*=8.8 Hz), 6.64 (1 H, d, *J*=2.5 Hz), 6.53 (1 H, d, *J*=2.5 Hz), 3.68 (3 H, s), 2.28 (3 H, s).

3,3-Bis-(4-hydroxy-phenyl)-1,3-dihydro-pyrrolo[2,3-b]pyridin-2-one (46)
LCMS m/z 319.27 $[M+H]^+$ @ R_T 0.97 min, 100%. δ_H (400 MHz, Methanol-D4) 8.10 (1 H, dd, *J*=4.9, 1.5 Hz), 7.55 (1 H, dd, *J*=7.3, 1.5 Hz), 6.93 - 7.11 (5 H, m), 6.71 (4 H, d, *J*=8.8 Hz).

6-Fluoro-3,3-bis-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one (47)
LCMS m/z 336.27 $[M+H]^+$ @ R_T 1.17 min, 100%. δ_H (400 MHz, Methanol-D4) 7.04 - 7.18 (1 H, m), 7.00 (4 H, d, *J*=8.80 Hz), 6.62 - 6.79 (6 H, m).

N-[3,3-Bis-(4-hydroxy-phenyl)-2-oxo-2,3-dihydro-indol-1-yl]-acetamide (48)
LCMS m/z 375.27 $[M+H]^+$ @ R_T 1.08 min, 100%. δ_H (400 MHz, Methanol-D4) 7.25 - 7.33 (1 H, m), 7.14 - 7.19 (1 H, m), 7.12 (1 H, dd, *J*=7.3, 1.0 Hz), 7.08 (4 H, d, *J*=8.8 Hz), 6.95 (1H, d, *J*=7.8 Hz), 6.69 (4 H, d, *J*=8.8 Hz), 2.17 (3 H, s).

5-[3,3-Bis-(4-hydroxy-phenyl)-7-methyl-2-oxo-2,3-dihydro-1H-indol-6-yloxy]-pentanoic acid methyl ester (49)
LCMS m/z 462.28 $[M+H]^+$ @ R_T 1.41 min, 97%.

5-[3,3-Bis-(4-hydroxy-phenyl)-7-methyl-2-oxo-2,3-dihydro-1H-indol-6-yloxy]-pentanoic acid (50)
LCMS m/z 448.32 $[M+H]^+$ @ R_T 1.13 min, 95%. δ_H (400 MHz, Methanol-D4) 7.01 (4 H, d, *J*=9.0 Hz), 6.86 (1 H, d, *J*=8.2 Hz), 6.67 (4 H, d, *J*=8.8 Hz), 6.56 (1 H, d, *J*=8.4 Hz), 3.97 (2H, t, *J*=5.1 Hz), 2.36 (2 H, t, *J*=6.4 Hz), 2.15 (3 H, s), 1.72 - 1.91 (4 H, m).

3,3-Bis-(4-hydroxy-phenyl)-6-methyl-1,3-dihydro-indol-2-one (51)
LCMS m/z 332.27 $[M+H]^+$ @ R_T 1.90 min, 100%. δ_H (400 MHz, Methanol-D4) 6.92 - 7.08 (5 H, m), 6.85 (1 H, d, *J*=8.3 Hz), 6.80 (1 H, s), 6.68 (4 H, d, *J*=8.8 Hz), 2.33 (3 H, s).

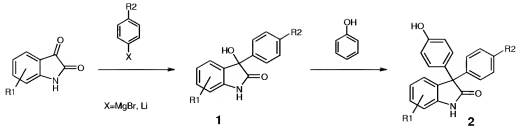
7-Chloro-3,3-bis-(4-hydroxy-phenyl)-6-methyl-1,3-dihydro-indol-2-one (52)
LCMS m/z 366.22 $[M+H]^+$ @ ~~1.93~~ R_T 1.93 min, 100%. δ_H (400 MHz, Methanol-D4) 7.00 (4 H, d, *J*=8.8 Hz), 6.96 (2 H, s), 6.69 (4 H, d, *J*=8.8 Hz), 2.36 (3 H, s).

5-Hydroxy-3,3-bis-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-indol-2-one (53)
LCMS m/z 348.26 $[M+H]^+$ @ R_T 1.55 min, 100%.

3,3-Bis-(4-hydroxy-phenyl)-6,7-dimethyl-1,3-dihydro-indol-2-one (54)
LCMS m/z 346.30 $[M+H]^+$ @ ~~1.85~~ R_T 1.85 min, 100%. δ_H (400 MHz, Methanol-D4) 7.00 (4 H, d, *J*=9.0 Hz), 6.84 (2 H, s), 6.67 (4 H, d, *J*=9.0 Hz), 2.27 (3 H, s), 2.22 (3 H, s).

Protocol F: Preparation of final products

General route for mono and mixed Friedel and Craft products *via* Grignard addition.

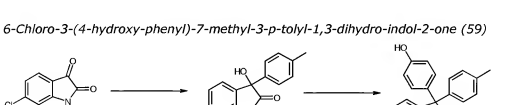


(a) Grignard Addition: To a stirred solution of isatin in dry tetrahydrofuran under nitrogen at -78°C was added 3 eq. of Grignard reagent or 3 eq. of a freshly prepared solution of organo-lithium reagent. After 30 min, the dry-ice bath was removed ~~and~~ the reaction was left to reach room temperature over 4 to 14 hours. To the reaction mixture was then added water, to quench excess Grignard reagent, acidified to pH 1-2 with 1N HCl, extracted with EtOAc (2x), dried over Na_2SO_4, filtered and concentrated to yield the crude products as yellowish viscous oils which were either purified over silica (eluted with a gradient of Heptane/EtOAc from 95-5 to 1-1) to yield the desired racemic mixture of compound of the type **1** as solids or taken to the next step without purification.

(b) Friedel and Craft reaction: To a crude solution of tertiary alcohol in dichloroethane was added phenol (5 eq.) and p-TSA (7.5 eq.). The reaction mixture was heated to 90°C for 3 hours and the reaction was cooled to room temperature. The solid (mainly insoluble p-TSA) was filtered off and washed (2x) with cold dichloroethane. The solution was concentrated and the remaining solid was purified over silica (eluted with a gradient of Heptane/EtOAc from 95-5 to 1-1) to yield the desired racemic mixture of product of the type **2** as solid.

The following compounds were all prepared according to Protocol F, unless otherwise specified.

6-Chloro-3-(4-hydroxy-phenyl)-7-methyl-3-p-tolyl-1,3-dihydro-indol-2-one (59)



Intermediate: LCMS (λ 215 nm, BDS-Hypersil C_{18}, 50 mm X 2.1 mm, 5 µ, 2.8 minute method ref: MET/CR/0720) m/z 270 $[M+H-H_2O]^+$ @ retention time 1.99 minute, 97%. *Final product (59):* LCMS (λ 215 nm, BDS-Hypersil C_{18}, 50 mm X 2.1 mm, 5 µ, 2.5 minute method ref: MET/CR/0720) m/z 364 $[M+H]^+$ @ retention time 1.64 minute, 100%. Overall

yield 87% over 2 steps. δ_H (400 MHz, Methanol-d4) 2.28 (3 H, s), 2.33 (3 H, s), 6.69 (2 H, d, *J*=8.8 Hz), 6.86-7.16 (8 H, m).

6-Chloro-3-(4-hydroxy-phenyl)-3-(4-methoxy-phenyl)-7-methyl-1,3-dihydro-indol-2-one (60)

Intermediate: LCMS (λ 215 nm, BDS-Hypersil C_{18}, 50 mm X 2.1 mm, 5 µ, 2.8 minute method ref: MET/CR/0720) m/z 286$[M+H-H_2O]^+$ @ retention time 1.92 minute, 100%. *Final product (60):* LCMS (λ 215 nm, BDS-Hypersil C_{18}, 50 mm X 2.1 mm, 5 µ, 2.5 minute method ref: MET/CR/0720) m/z 380 $[M+H]^+$ @ retention time 1.57 minute, 100%. Overall yield 60% over 2 steps. δ_H (400 MHz, Methanol-d4) 2.34 (3 H, s), 3.75 (3 H, s), 6.69 (2 H, d, *J*=8.8 Hz), 6.83 (2 H, d, *J*=9.3 Hz), 6.91-7.02 (3 H, m), 7.04-7.14 (3 H, m).

6,7-Difluoro-3-(4-hydroxy-phenyl)-3-p-tolyl-1,3-dihydro-indol-2-one (57)

Intermediate: LCMS (λ 215 nm, BDS-Hypersil C_{18}, 50 mm X 2.1 mm, 5 µ, 2.8 minute method ref: MET/CR/0720) m/z 258$[M+H-H_2O]^+$ @ retention time 1.96 minute, 96%. *Final product:* LCMS (λ 215 nm, BDS-Hypersil C_{18}, 50 mm X 2.1 mm, 5 µ, 2.8 minute method ref: MET/CR/0720) m/z 352 $[M+H]^+$ @ retention time 2.06 minute, 98%. Overall yield 57% over 2 steps. δ_H (250 MHz, $CDCl_3$) 2.31 (3 H, s), 4.76 (1 H, s), 6.60-6.97 (4 H, m), 7.03-7.15 (6 H, m), 7.55 (1 H, s).

6,7-Difluoro-3-(4-hydroxy-phenyl)-3-(4-methoxy-phenyl)-1,3-dihydro-indol-2-one (58)

Intermediate: LCMS (λ 215 nm, BDS-Hypersil C_{18}, 50 mm X 2.1 mm, 5 µ, 2.8 minute method ref: MET/CR/0720) m/z 274$[M+H-H_2O]^+$ @ retention time 1.81 minute, 97%. *Final product (58):* LCMS (λ 215 nm, BDS-Hypersil C_{18}, 50 mm X 2.1 mm, 5 µ, 2.8 minute method ref: MET/CR/0720) m/z 368$[M+H]^+$ @ retention time 1.99 minute, 94%. Overall yield 14% over steps.

3-(4-Benzyloxy-phenyl)-6-chloro-3-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-indol-2-one

Intermediate: LCMS (λ 215 nm, BDS-Hypersil C_{18}, 50 mm X 2.1 mm, 5 µ, 2.8 minute method ref: MET/CR/0720) m/z 362$[M+H-H_2O]^+$ @ retention time 2.16 minute, 88%. δ_H (400 MHz, Methanol-d4) 2.32 (3 H, s), 5.05 (2 H, s), 6.93 (2 H, d, *J*=8.8 Hz), 6.96-7.02 (1 H, m), 7.03-7.13 (1 H, m), 7.20-7.46 (7 H, m). *Final product:* LCMS (λ 215 nm, BDS-Hypersil C_{18}, 50 mm X 2.1 mm, 5 µ, 2.5 minute method ref: MET/CR/0720) m/z 456$[MH]^+$ @ retention time 1.59 minute, 100%. Overall yield 11% over 2 steps. δ_H (400 MHz, Methanol-d4) 2.31 (3 H, s), 3.83 (2 H, d, *J*=2.5 Hz), 6.60 - 6.72 (3 H, m), 6.77 - 6.89 (3 H, m), 6.91 - 7.21 (9 H, m).

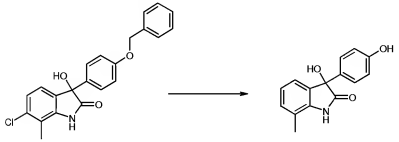
3-(4-Benzyloxy-phenyl)-6,7-difluoro-3-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one

Intermediate: LCMS (λ 215 nm, BDS-Hypersil C_{18}, 50 mm X 2.1 mm, 5 µ, 2.8 minute method ref: MET/CR/0720) m/z 350$[M+H-H_2O]^+$ @ retention time 2.07 minute, 94%. δ_H (400 MHz, Methanol-d4), 5.06 (2 H, s), 6.82 - 7.01 (4 H, m), 7.24-7.31 (3 H, m), 7.34 (2 H, t, *J*=7.3 Hz), 7.38-7.45 (2 H, m).

Final product: LCMS (λ 215 nm, BDS-Hypersil C_{18}, 50 mm X 2.1 mm, 5 µ, 2.8 minute method ref: MET/CR/0720) m/z 444$[M+H-H_2O]^+$ @ retention time 2.03 minute, 88%. Overall yield 24% over 2 steps.

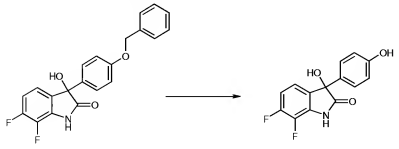
Protocol G – Debenzylation/dehalogenation

3-Hydroxy-3-(4-hydroxy-phenyl)-7-methyl-1,3-dihydro-indol-2-one



A clean sample of tertiary alcohol (40.9 mg), Pd/C (10 wt %) in methanol was submitted to hydrogenation conditions. The reaction was monitiored by LCMS. After 14h at room temperature, the palladium on charcoal was filtered off and washed with methanol. The combined organic layer were concentrated, and the crude product was purified by silica (with a gradient of Heptane/EtOAc from 85-15 to 1-1) to yield the racemic target compound (4.5 mg, 16% yield) as a solid. LCMS (λ 215 nm, BDS-Hypersil C_{18}, 50 mm X 2.1 mm, 5 µ, 2.5 minute method ref: MET/CR/0720) m/z 238$[M+H-H_2O]^+$ @ retention time 1.26 minute, 100%

6,7-Difluoro-3-hydroxy-3-(4-hydroxy-phenyl)-1,3-dihydro-indol-2-one



A clean sample of tertiary alcohol (41.8 mg), Pd/C (10 wt %) in methanol was submitted to hydrogenation conditions. The reaction was monitiored by LCMS. After 14h at room temperature, the palladium on charcoal was filtered off and washed with methanol. The combined organic layer were concentrated, and the crude product was purified by silica (with a gradient of Heptane/EtOAc from 85-15 to 1-1) to yield the racemic target compound (5.5 mg, 17% yield) as a solid. LCMS (λ 215 nm, BDS-Hypersil C_{18}, 50 mm X 2.1 mm, 5 µ, 2.5 minute method ref: MET/CR/0720) m/z 260$[M+H-H_2O]^+$ @ retention time 1.29 minute, 100%.

Example 2: Cell proliferation

Inhibition of the proliferation of human cancer cells is widely used to predict the anti-cancer potential of novel chemicals. Typically, human cancer cell lines derived from tumour material are maintained in monolayer cultures and test chemicals are added for varying durations. Test compounds with anti-cancer potential are expected to reduce proliferation and thereby reduce cell number relative to vehicle treated control cell cultures. Cell number can be monitored by cell counting, determining metabolic rate (e.g. metabolic reduction of tetrazolium salts such as (3-(4,5-dimethylethiazol-2-yl)-2,5-diphenyltetrazolium bromide or Alamar Blue), quantifying DNA content (using DNA binding dyes such as BODIPY-FL-14-dUTP) or measuring nucletotide incorporation into DNA (e.g. radiolabelled thymidine or bromo-deoxyuridine incorporation).

One important consideration is whether any inhibitory effects of test compounds are specific to cancer cell proliferation or are due to general inhibition of cell proliferation. This issue can be addressed using paired cell lines; for example, the effects of test compounds on the proliferation of transformed cancer cell lines can be compared with the effects of test compounds on the proliferation of untransformed cells from the same tissue source. Alternatively, phenotypic differences between cancer cell lines can be exploited to evaluate the selectivity of test compounds. For example, the anti-proliferative effects of some compounds are only apparent in certain sub-types of human breast cancer cell lines (e.g. breast cancer cell lines with PTEN gene mutations or gene amplification of the p70S6K protein kinase), but not in breast cancer cell lines that do not exhibit this phenotype (Noh et al. (2004) Clinical Cancer Research 10, 1013-1023; Yu et al. (2001) Endocrine-Related Cancer 8, 249-258). The selectivity of test compounds in the latter models is associated with the mechanism of compound action and is related to the presence, absence or relative abundance of the protein target of the test compound in the relevant cell lines.

Method

Compound effects were evaluated on the proliferation of MDA-468 and MDA-231 human breast cancer cells. Cells were maintained in growth medium: RPMI 1640 containing 10% foetal bovine serum and 1% pen/strep. Cells were split 1:4 or 1:8 twice a week when 90% confluent. For the cell proliferation assay, cells were plated at 8000 cell/well into 96 well black Packard Viewplates in growth medium. After 1 day, the growth medium was replaced with growth medium containing test compounds or vehicle, and cells were maintained in culture for a further 2 days. Growth medium was then removed and replaced with 150 µl of alamarBlue in RPMI medium containing 1% pen/strep. Following 120 minutes incubation at 37ºC, fluorescent intensity was read using a plate reader.

Results

The concentration (in micromolar) of compounds of general formula (I) required to inhibit the proliferation of MDA-468 and MDA-231 human breast cancer cells by 50% (IC_{50}) are shown in Figure 1. The results shown in Figure 1 demonstrate the ability of the compounds of the general formula (I) to inhibit the proliferation of MDA-468 human breast cancer cells at lower concentrations ~~as~~than those required to inhibit proliferation of MDA-231 human breast cancer cells.

Example 3: Protein synthesis studies

The purpose of these studies ~~as~~was to investigate whether compounds of the general formula (I) have effect on protein synthesis, measured as ^{14}C-Leucine uptake or incorporation into ~~proteins. As~~proteins, as described in "Leucine Uptake [^{14}C] Cytostar-T assay, Amersham Biosciences" (CFA773).

MDA-MB-231 and MDA-MB-468 cells were seeded at 8000 cells/well in CytoStar-T 96-well ~~microplates. And~~microplates and incubated overnight in growth medium. The next day medium was carefully aspirated (8-channel Vacuboy) and 50 µL of fresh pre-warmed medium (10% FCS, 10 mM HEPES pH 7.2 – 7.5) was added. Cells were allowed to equilibrate at 37 °C for 60 min. Test compounds were added in 50 µL medium and ^{14}C-leucine was added in 100 µL medium (0.5 µCi mL-1 final). Plates were sealed with transparent, adhesive foil. Plates were then incubated ~~in oat~~ 37°C for 6h in a humidified incubator. Incorporation of radioactive leucine into proteins (a measure of protein synthesis) was then read by coincidence scintillation (counts per minute (CPM)) using a Wallac Microbeta detector at the indicated

time-intervals. A reading a t=0 (5 min after sealing plates) for each well is subtracted as background.

The results are shown in Figure 2 measured after 6 hours.

The results indicate that Compound 3 significantly inhibits ^{14}C-Leucine incorporation in MDA-MB-468 in a concentration dependent manner observed after 240 min compound incubation and up to 22 hours. IC_{50} is estimated to be 100 nM (240 min to 22 hours). Interestingly, the effect seems to reach a plateau at the high concentrations corresponding to approx. 1/6 of total incorporated. This indicates that there is some proportion of the protein synthesis that Compound 3 is not able to affect.

No significant effect of Compound 3 was observed in MDA-MB-231 up to 430 min. At 22 hours a minor effect is observed at 30 µM. IC_{50} >> 30 µM (22 hours).

The inhibitory effect of Compound 3 is therefore very specific ~~for~~to MDA-MB-468.

The control compounds Anisomycin and Cycloheximide (not shown) completely ~~inhibit~~inhibited ^{14}C-Leucine incorporation in both cell lines at all time-points (as opposed to Compound 3, see above).

Example 4: Western Blot Studies

To investigate the mechanism of action of compounds of general formula (I), Western Blot studies were performed to investigate the activation state of pathways linked to the regulation of protein synthesis (see Figure 4 and 5).

Method

MDA-MB-468 cells (also called MDA-468) or MDA-MB-231 (also called MDA-231) were kept in culture and plated at 400,000 cells/well in 6 well cell culture plate. 16-24 hours after, the growth medium ~~were~~was shifted to growth medium containing subject compounds.

After 24 or 48 hours incubation with compounds, cells were washed with ice cold PBS buffer and harvested in lysis buffer: Cytobuster reagent (Novagen) containing phosphatase inhibitor cocktail 1 and 2 and protease inhibitor cocktail (Sigma). Samples containing an equal amount of protein were loaded onto 7% Tris Acetate gels, 10% Bis-Tris in MES buffer or 12% Bis-Tris

gels using MOPS running buffer (Invitrogen). Following electrophoresis the samples were blotted onto a PVDF membrane (Invitrogen). For membrane blocking and antibody incubations of p70 S6K, Phospho-p70 S6K (Thr389), PathscanI and S6 antibodies (Cell Signalling Technology) a buffer containing 0.2% Tween-20, 5% non-fat dry milk, 5% FBS, in Tris buffered Saline (TBS) were used. For immunoblotting of 4EBP1, Phospho 4EBP1 (Thr37/46), Phospho 4EBP1 (Ser65) (Cell Signalling Technology) and Cyclin D3 (Santa Cruz), a protocol from Cell Signalling Technology ~~were~~was used. Cell Signalling Technology blocking buffer contains 0.1% Tween-20, 5% non fat dry milk in TBS and primary antibody dilution buffer contains 0.1% Tween-20, 5% BSA in TBS. Before adding primary antibody dilution buffer to the membranes, the blots were rinsed briefly in 0.1% Tween-20. All antibody incubations were done overnight at 4°C~~ overnight~~. After washing the membranes with 0.1% Tween-20 in TBS, the blots were incubated with horseradish peroxidase conjugated anti-Rabbit IgG (1:1000-1:3000; Amersham Biosciences) at room temperature for 1 hour. Peroxidase activity was detected using the ECL detection system (Amersham Biosciences).

Results

Western blot analyses demonstrate that compounds of general formula (I), such as Compound 3 (lanes 2 and 3), inhibit the phosphorylation of p70S6K and S6 ribosomal protein in MDA-468 cells following 24 hour incubation (Figure 4). Similar effects are observed with the mTOR inhibitor, rapamycin (lane 5) and the PI3 kinase inhibitor LY294002 (lane 6). AKT phosphorylation on Ser473 is not inhibited by Compound 3 or rapamycin, whereas LY294002 inhibits the phosphorylation of AKT on Ser473. Furthermore, Compound 3 induces a gel mobility shift in 4E-BP1 as shown using both total and thr37/46 phospho-specific anti-4E-BP1 antibodies, indicative of an alteration in the phosphorylation status of 4E-BP1. This is confirmed by the inhibitory effect of Compound 3 on the phosphorylation of ser65 of 4E-BP1. Similar effects are observed with the mTOR inhibitor, rapamycin and the PI3 kinase inhibitor LY294002. In addition, expression of the cell cycle regulatory protein cyclin D3 is reduced by Compound 3, rapamycin and LY294002. These data suggest that mammalian homologue of TOR (mTOR) kinase is active in MDA-468 cells under growth conditions, leading to phosphorylation of mTOR target proteins such as p70S6 kinase (p70S6K) and 4EBP1, and downstream regulation of protein synthesis and cell proliferation via S6 ribosomal protein, eukaryotic translation initiation factor, eIF4, and cyclin D3. Compounds of general formula (I), such as Compound 3, as well as rapamycin and LY294002, inhibit this pathway in MDA-468 cells and might be expected to reduce protein synthesis and cell proliferation.

Compound 3 (lane 2) did not inhibit the phosphorylation of p70S6K, or induce a gel mobility shift in total p70S6K, in MDA-231 cells following 48 hour incubation (Figure 5). In contrast,

rapamycin (lane 5) and LY294002 (lane 6) inhibit the phosphorylation of p70S6K, and induce a gel mobility shift in total p70S6K, following 48 hour incubation in MDA-231 cells. Compound 3, rapamycin and LY294002 all inhibit the phosphorylation of p70S6K and induce a gel mobility shift in total p70S6K in MDA-468 cells following 48 hour incubation, demonstrating a cell selective effect of compounds of general formula (I), such as Compound 3.

Example 5: Prostate Tumour Xenograft studies (Human PC3M cell line)

The purpose of this study was to evaluate whether compounds of general formula (I), such as Compound 3, inhibit the growth of cancer cells in a xenograft animal model.

Method

Male nude NMRU nu/nu mice weighing 25-45 grams ~~are~~were implanted with PRXF PC3M tumours by subcutaneous implantation in both flanks. Compound 3 (50 & 100 mg) ~~is~~was administered daily by the per-oral (PO) route in an appropriate vehicle (2% DMSO:5% Tween 80: 93% saline) either alone or in combination with a sub-optimal dose of paclitaxol (10mg/kg ; intravenous; given once/week). Tumor volume ~~is~~was determined once or twice/week for a period of 17 days.

Results

Compound 3 reduces the rate of tumour cell growth when given as a monotherapy (see Figure 6). Furthermore, additive anti-growth effects are noted in combination with paclitaxol.

Example 6: Effect of Compound 3 on Cell Proliferation of Breast, Prostate and Colon Cancer Cell Lines

Methods:

Cell culture: All cell lines except MCF10A are maintained in RPMI medium containing 10% foetal Bovine Serum (FBS) 100 U/ml penicillin, and 100 µg/ml streptomycin. MCF10A is maintained in mammary epithelial growth medium (MEGM) with singlequot addition (BPE, hydrocortisone, hEGF, insulin, gentamicin/amphotericin-B) (Clonetics/Cambrex Bio Science). All cell lines are incubated at 37°C, 5% CO_2, and 95% humidity.

Alamar Blue cell proliferation assay: Cells are plated in black cell culture treated Packard/Perkin Elmer 96-viewplates in 100 µl/well RPMI medium containing 10% FBS, 100 U/ml penicillin, and 100 µg/ml streptomycin. Cell proliferation has been estimated in triplicate for all cell lines in medium containing either 1% FBS or 10% FBS. Cell densities are estimated based on growth during the assay to 80-90% confluency, and are shown in Table 1. The day after plating, the growth medium is changed to either 100 µl/well RPMI containing 1% FBS, 100 U/ml penicillin, 100 µg/ml streptomycin and 25 µg/ml gentamicin or to 100 µl/well RPMI containing 10% FBS, 100 U/ml penicillin, 100 µg/ml streptomycin and 25 µg/ml gentamicin. Compounds are added in 9 point half-log dilution series at concentrations indicated in the graphs. All data based on multiple determinations have been aggregated according to business rules standard to a person skilled in the art. Furthermore, two dilution formats have been used to determine the IC_{50} values: (1) The standard ~~condition~~conditions are 9 half-log dilutions starting from 32 µM; and (2) if the compound IC_{50} <100 nM, 9 half-log dilutions starting from 3.2 µM have been used. Briefly, compounds are diluted in compound plates in growth medium containing either 1% FBS or 10% FBS corresponding to the medium in the plates. Compounds are transferred to the cell plates by transfer of 100 µl/well, resulting in a total volume of 200 µl/well containing compound at concentrations indicated in graphs and 0.25% DMSO. Terfenedine is used as a control for maximal cell kill in wells containing 50 µM terfenedine and 0.5% DMSO (Smax). Negative control wells (So) contain medium with 0.25% DMSO.

After compound addition cell plates are incubated undisturbed for 72 hours at 37°C, 5% CO_2, and 95% humidity.

The number of viable cells is estimated using an Alamar Blue assay that measures mitochondrial activity. The medium is decanted and replaced with 150 µl/well RPMI medium without phenol-red containing 100 U/ml penicillin, and 100 µg/ml streptomycin and 10% Alamar Blue. The plates are placed in the incubator at 37°C, 5% CO_2, and 95% humidity for 2 hours. Then, plates are moved to a table and allowed to cool to room temperature without stacking the plates. Alamar Blue signal is read in a fluorescence plate reader using a 590 nm emission filter and a 530 nm ~~exitation~~excitation filter.

Data handling/calculations: Data are normalised to values from 0% activity (S_0) to 100% activity (S_{max}). Average values for S_0 and S_{max} are calculated and used to calculate percent activity (PCTACT) in the assays by the formula: $PCTACT=(X_{raw}-S_{max})/(S_0-S_{max})*100$.

Z'-values for assay plates are calculated by:

$Z'=1-3*(STDEV(S_0)+STDEV(S_{max}))/(S_0-S_{max})$. ~~In~~On aveage Z'~0.8 and always above 0.6.

Sigmoidal curve fitting is done using Prism using the equation: Y=Bottom + (Top-Bottom)/(1+10^((LogIC$_{50}$-X)*HillSlope)).

Table 1. Cell densities at plating in 96-well plates

Cell line	Cancer	Cells/well in 1% FBS	Cells/well in 10% FBS
MDA-MB-231	Breast	6000	4000
MDA-MB-435S	Breast	10000	5000
MDA-MB-453	Breast	3000	2000
MDA-MB-468	Breast	6000	4000
SKBr-3	Breast	7000	6000
BT-474	Breast	10000	10000
BT-549	Breast	6000	5000
MCF-7	Breast	5000	5000
T-47D	Breast	5000	5000
ZR75-1	Breast	7000	7000
HCC-1954	Breast	5000	2500
MCF-10A	Normal breast epithelial cells	18000 (MEGM medium)	
PC-3	Prostate	-	3000
PC-3/M	Prostate	-	3000
DU-145	Prostate	-	1250
LnCaP	Prostate	-	8000
Colo205	Colon	-	5000

Results:

All cell lines are run in cell proliferation in medium containing either 1% serum or 10% serum, both estimations in triplicate. Percent activity (PCTACT) in the assays, equal to percent inhibition of growth, is calculated as described in Methods.

Table 2 summarizes the IC$_{50}$ values for cell proliferation inhibition of the cell lines. IC$_{50}$ values refer to the concentration of compound required to inhibit cell proliferation by 50%. Cell proliferation curve fits are shown in Figures 7 to 14.

Breast cancer cell lines: A broad panel of breast cancer cell lines ~~have~~has been tested for their sensitivity to Compound 3 as well as Compound 21 and ~~oxyphenisatine~~oxyphenisatine. The tested cell lines fall into two very clear categories. 1) Cell lines that are sensitive to Compound 3. Cell proliferation IC$_{50}$ values range from 0.6 nM to 30 nM when assayed in 1% FBS and between 15 and 80 nM when assayed in 10% FBS. These include the breast cancer cell lines T47-D, MCF-7, MDA-MB-453, MDA-MB-468, BT-474, SKBr-3, BT-549, and HCC-1954 grown under both high (10% FBS) and low (1% FBS) serum conditions. 2) Cell lines

that are insensitive to Compound 3 with IC_{50} values above 3 μM. These include MDA-MB-231, MDA-MB-435S and ZR75-1 grown under both high (10% FBS) and low (1% FBS) serum conditions. The non-transformed breast epithelial cell line, MCF10A, is also insensitive to Compound 3.

Percent activity relative to growth inhibition with 50 μM terfenedine ranged from 60% to 90% growth inhibition. In general the cell lines are more sensitive to the compound under low (1% FBS) serum conditions than under high (10% FBS) serum conditions. The most sensitive breast cancer line is MDA-MB-453.

Two other compounds in the series have also been tested, Compound 21 and oxyphenisatine. Both compounds have exactly the same cell line anti-proliferative profile as Compound 3, but are slightly lower in potency (compare Figures 9, 10 and 11).

The results are summarized in Table 2 and Figures 7-11.

Prostate cancer cell lines: The DU-145, PC-3, PC-3/M and LnCaP prostate cancer cell lines have been tested in cell proliferation assays. PC-3 is highly sensitive to Compound 3, while LnCaP is less sensitive, and PC-3/M and DU-145 are insensitive. Compound 21 and oxyphenisatine have the same cell line sensitivity profile, however, these compounds have lower potency than Compound 3. The results are summarized in Table 2 and Figure 12. The effect of Compounds 41 and 35 was also compared with Compound 3; both compounds inhibit the proliferation of the PC3 human prostate cancer cell line (Figure 13).

Colon cancer cell lines: The colon cancer cell line Colo205 has been tested in a cell proliferation assay with Compound 3 resulting ~~orin~~ in IC_{50} = 66 nM. The results are summarized in Table 2 and Figure 14.

Table 2. Summary table of IC_{50} values for inhibition of cell proliferation.

Cell line	Cancer	3		21	Oxyphenisatine
		1% FBS EC50 (nM)	10% FBS EC50 (nM)	10% FBS EC50 (nM)	10% FBS EC50 (nM)
T47-D	Breast	11	37	83	324
MCF7	Breast	24	74	85	517
MDA-MB-435S	Breast	>3000	>3000	>3000	>3000
MDA-MB-453	Breast	4	18	38	228
MDA-MB-468	Breast	14	48	138	935
MDA-MB-231	Breast	>3000	>3000	>3000	>3000
BT-474	Breast	13	37	85	324
SKBr-3	Breast	12	43	95	527
BT-549	Breast	18	68	131	859
ZR75-1	Breast	>3000	>3000	>3000	285
HCC-1954	Breast	27	84	119	912
MCF10A	Normal breast epithelial	>3000		>3000	>3000
PC-3	Prostate	-	87	138	899
LnCaP	Prostate	-	235	233	790
DU-145	Prostate	-	>3000	>3000	>3000
PC-3/M	Prostate	-	>3000	>3000	>3000
Colo205	Colon	-	66	-	-

Notes: IC_{50} values are shown in nanomolar concentration. Growth inhibition (PCTACT) lower than 20% is considered insignificant. MCF10A cells are maintained in serum-free MEGM medium. Values are calculated by Prism.

Example 7: Xenograft studies using MDA-MB-468 tumours

The purpose of this study was to evaluate whether compounds of general formula (I), such as Compounds 3 and 41, inhibit the growth of tumours derived from MDA-MB-468 breast cancer cells (hormone insensitive human breast cancer cells) in a xenograft animal model.

Method

Nude balb/c mice weighing 25-45 grams ~~are~~were implanted with MDA-MB-468 tumours by subcutaneous implantation in both flanks. Compounds 3 and 41 ~~are~~were administered either daily for 15 days by the per-oral (PO) route (50 & 100mg) in an appropriate vehicle (2% DMSO:5% Tween 80: 93% saline) or weekly for 4 weeks by the intravenous (IV) route (25 &

50mg/kg) in an appropriate vehicle (2% DMSO:5% Tween 80: 93% saline). Tumour volume ~~is~~was determined once or twice/week.

Results

Compound 3 ~~reduces~~reduced the rate of MDA-MB-468 tumour cell growth in a dose related manner when given as a monotherapy either by the PO or IV route (see Figure 15). Furthermore, tumour regression ~~is~~was noted using the higher doses of Compound 3. Intravenous dosing with Compound 3 appeared to be more effective than per-oral dosing (Figure 15). Compound 41 ~~is~~was more effective than Compound 3, inducing a more pronounced tumour regression at all doses tested (Figure 16). Furthermore, Compound 41 was equally effective by per-oral and intravenous dosing (Figure 16). Compound 41 also appeared to be more effective than paclitaxel in these studies (Figure 16).

Example 8: Xenograft studies using MCF-7 tumours

The purpose of this study was to evaluate whether compounds of general formula (I), such as Compound 41, inhibit the growth of tumours derived from MCF-7 breast cancer cells (hormone responsive human breast cancer cells) in a xenograft animal model.

Method

Nude balb/c mice weighing 25-45 grams ~~are~~were implanted with MCF-7 tumours by subcutaneous implantation in both flanks. Compounds 3 and 41 ~~are~~were administered either daily for 15 days by the per-oral (PO) route (20 & 100mg) in an appropriate vehicle (2% DMSO:5% Tween 80: 93% saline) or weekly for 4 weeks by the intravenous (IV) route (10 & 50mg/kg) in an appropriate vehicle (2% DMSO:5% Tween 80: 93% saline). Tumour volume ~~is~~was determined once or twice/week.

Results

Compound 41 ~~reduces~~reduced the size of MCF7 tumours when given as a monotherapy either by the PO or IV route (see Figure 17). Furthermore, tumour regression ~~is~~was noted using all doses tested. The effect of Compound 41 ~~appears~~appeared to be greater than paclitaxel in ~~thjis~~this model (Figure 17). Compound 41 was equally effective by the per-oral and intravenous dosing.

Example 9: Activation of caspase activity

The purpose of this study was to evaluate whether compounds of general formula (I), such as Compound 3, affect caspase activity as a marker of apoptosis, a form of cell death. Both short-term, medium-term and long-term effects of Compound 3 ~~are~~were assessed by measuring caspase activity at 4, 6 and 22 hours post compound addition.

Method

Human breast cancer cell lines ~~are~~were seeded at 8000 cells/ well in 96-well black Packard Viewplates and maintained in RPMI medium containing 10% foetal Bovine Serum (FBS) 100 U/ml penicillin, and 100 µg/ml streptomycin overnight at 37 °C, 5% CO_2 in a humidified incubator. Compounds such as Compound 3 ~~are~~were then added to the well and caspase activity ~~is~~was measured at various timepoints using a Caspase activity kit (fluorogenic "Apo-ONE® Homogeneous Caspase-3/7 Assay" kit, #G7791; Promega) according to the manufacturers instructions. Fluorescence intensity (485/535 nm) ~~is~~was measured using on EnVision platereader. Reagent background values (mean of all 8 wells) ~~are~~were subtracted from the experimental wells.

Results

Addition of Compound 3 for 6 hours ~~activates~~activated caspase activity in human breast cancer cell lines that ~~are~~were sensitive to the anti-proliferative effects of Compound 3 (Figure 18), although no activation ~~is~~was noted in MDA-468 cells. Activation of caspase activity ~~is~~was not observed in breast cancer cell lines that ~~are~~were insensitive to the anti-proliferative effect of Compound 3.

These results suggest that compounds of general formula (I), such as Compound 3, may induce apoptotic cell death in certain human breast cancer cell lines.